Tilburg University

The 'rehabilitating' effect of sounds

de Boer-Schellekens, L.

Publication date:
2013

Document Version
Publisher's PDF, also known as Version of record

Link to publication in Tilburg University Research Portal

Citation for published version (APA):
de Boer-Schellekens, L. (2013). *The 'rehabilitating' effect of sounds: Studies on audiovisual integration in autism, schizophrenia, dyslexia and aging*. Ridderprint.

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

Take down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Download date: 12. May. 2021

The 'rehabilitating' effect of sounds

Studies on audiovisual integration in autism, schizophrenia, dyslexia and aging

The 'rehabilitating' effect of sounds: Studies on audiovisual integration in autism, schizophrenia, dyslexia and aging.

© Copyright, Liselotte de Boer-Schellekens, The Netherlands, 2013

All rights reserved. No part of this thesis may be reproduced, stored in a retrieval system, or transmitted in any form or by any means without the written permission from the author.

ISBN:	978-90-5335-743-9
Cover design:	Drukkerij Ridderprint, Ridderkerk
Lay-out:	Karin Berkhout
Printing:	Drukkerij Ridderprint, Ridderkerk

The 'rehabilitating' effect of sounds

Studies on audiovisual integration in autism, schizophrenia, dyslexia and aging

Proefschrift

ter verkrijging van de graad van doctor aan Tilburg University op gezag van de rector magnificus, prof. dr. Ph. Eijlander, in het openbaar te verdedigen ten overstaan van een door het college voor promoties aangewezen commissie in de aula van de Universiteit op vrijdag 1 november 2013 om 14:15 uur

door

Liselotte Wilhelmina Zofia de Boer-Schellekens

geboren op 2 april 1975 te Breda

Promotor

Prof. dr. J.H.M. Vroomen

Copromotor

Dr. M.N. Keetels

Promotiecommissie

Prof. dr. C. Kemner
Prof. dr. M.M. Sitskoorn
Dr. D. Talsma

Voor Morten, Tiemen en Josefiene

Contents

Chapter 1

Introduction

People are social human beings whose everyday lives are characterized by social interaction and communication. In general, we take this social aspect of life for granted and we assume that the people we interact with share the same perceptual experiences. The question however is, whether this sharing of perceptions is as self-explanatory as we think? In a social environment, events typically involve stimulation through multiple sensory modalities. For example, a talker can be heard and seen at the same time. This results in an ensemble of multiple features across the different senses that our brain has access to (i.e., lip movement, facial expression, speed and temporal structure of the speech sound) that ultimately leads to an increase in perceptual reliability. During everyday life, our brain thus has to synthesize a mix of sensory information into one coherent multisensory percept. This sensory synthesis, also referred to as Multisensory Integration (MSI) is a constantly occurring phenomenon that shapes our view of the world and is therefore crucial for our everyday, social and adaptive behavior (Wallace, 2004). Besides questions of how our brain integrates this wealth of sensory information and how a coherent representation of the world is obtained (Keetels & Vroomen, 2012), a crucial issue concerning MSI is what happens if the brain is impaired in integrating this mix of sensory input.

The importance of clinical MSI research

In the last decade, research on MSI has been growing, resulting in a wealth of data to gain insights into the mechanisms by which the brain deals with and benefits from multisensory inputs. This research is, however, mostly performed on 'healthy', 'normal' or 'typically developing' participants with no serious history of medical, psychiatric or neurological illness, trauma or use of medication affecting the nervous system and with normal, or corrected-to-normal hearing and seeing. Without a doubt, this wealth of MSI data from 'healthy' people is invaluable for the improvement of our knowledge on how our sensory system(s) work(s) and the ubiquity of multisensory influences on apparently unisensory events (e.g., the 'McGurk illusion', McGurk & MacDonald, 1976). However, surprisingly, exertions to translate this elementary MSI knowledge into translational clinical efforts are limited, although studies on the mechanisms of MSI have clear clinical implications (Foxe & Molholm, 2009). Fortunately, in the last years, research on MSI in clinical, neurological or psychiatric populations is rising, and clinical findings have also helped to elucidate the substantial interdependence of the sensory domains (Kerkhoff, 1999; Kerkhoff, Artinger, & Ziegler, 1999). The importance of research on MSI in clinical and/or psychiatric populations can easily be gathered from our (human) communication and social interaction, as in a social environment, events typically involve stimulation through multiple sensory modalities (e.g., in speech, in most cases, we can see and hear somebody talk). Integration of these stimuli enables us to better understand the social intentions of others. If people have difficulties with, for example, integrating visual and auditory information, one could imagine that such MSI impairments may play an important role in the atypical behavior of individuals, as these individuals experience a possible aberrant percept of what the other says or means (which is, for example, seen in individuals with Autism Spectrum Disorder or schizophrenia). Obviously, to better understand the atypical behavior (not only socially) of clinical or psychiatric populations, we should take a closer look at the mechanisms and/or impairments that may underlie this aberrant behavior. For both Autism Spectrum Disorder (ASD) and schizophrenia, sensory deficits have often been reported and empirical evidence for these impairments is growing. To relate these deficits to deviant social behavior, for example, theories on ASD hypothesize that sensory deficits might have downstream effects on the development of the perceptual system that may eventually lead to adverse consequences for communication and social interaction (Bertone, Mottron, Jelenic, & Faubert, 2005; Mottron & Burack, 2001).

This thesis discusses MSI in people with ASD, schizophrenia or dyslexia. These groups of participants were chosen for several reasons. First of all, as described above, there is empirical and clinical evidence that people with ASD and schizophrenia show sensory deficits. These deficits may cause MSI problems that underlie aberrant social behavior. However, increasing MSI research in ASD and schizophrenia has mainly focused on the integration of higher-order information like speech or emotions. There is relative less evidence of the integration (problems) of low-level stimuli in ASD and schizophrenia and findings so far are not consistent. Hopefully, the studies on ASD and schizophrenia in this thesis will contribute to a better understanding of low-level audiovisual integration. Third, research on developmental dyslexia has shown that the integration of audiovisual information is undoubtedly a critical process in the development of linguistic skills (especially reading, Hairston, Burdette, Flowers, Wood, & Wallace, 2005). Unfortunately, research on MSI in developmental dyslexia is limited, although there is evidence that people with dyslexia show altered performance on (audio)visual temporal order tasks (e.g., Hairston et al., 2005; Hari, Renvall, & Tanskanen, 2001; Jáskowski & Rusiak, 2008). Therefore, the processing of audiovisual information in this widespread learning disorder was examined in this thesis. At last, MSI seems to be subject to developmental changes during typical developmental life hood. More knowledge of this developmental perspective on MSI might be of great value for clinical and learning disorders as well, as it could provide knowledge on underlying development of structures and mechanisms that may be altered in ASD, schizophrenia and/or dyslexia. As most developmental evidence comes from studies on infants and children, studies in the more elderly could provide more complementary knowledge on this topic. From this developmental perspective, MSI was studied in various age groups to examine possible (audiovisual) integration differences related to age. In sum, the studies in this thesis on low-level audiovisual integration in individuals with ASD, schizophrenia and dyslexia and in aging will contribute to the knowledge on underlying mechanisms and constraints under which information from different modalities is combined in these different groups of participants.

Throughout this thesis, the term 'study groups' will be used to refer to the groups of participants with ASD, schizophrenia and dyslexia and the elderly as an entity. This term is chosen, because there is no specific 'umbrella' term (like clinical or psychiatric) to address all of the participants in an appropriate manner. These 'study groups' do not include the control groups that participated in the studies. These are referred to as 'control groups'.

Important issues on MSI

Temporal synchrony

In research on MSI, it is generally agreed that temporal synchrony is *the* most important factor for MSI to occur (e.g., Radeau, 1994; Stein & Meredith, 1993; Welch & Warren, 1980). This means that intersensory integration will only occur if information from the different sensory modalities arrives at approximately the same time in the brain. If not, two separate events are perceived. There are, however, neuronal and non-neuronal factors that influence the arrival and processing time of two or more sensory signals to the brain, even though those signals may have emanated simultaneously from a given distal source (King & Palmer, 1985; Pöppel, Schill, & Von Steinbüchel, 1990). The factors that lead to the physical asynchrony of proximal multisensory events mainly deal with differences in physical and neural transmission times between the different senses (Vatakis, 2013). In order to perceive synchrony, the brain thus needs to deal with differences in physical and neural transmission times between the different senses. For example, sounds travel much slower through air than visual information (i.e., 300,000,000 ms for vision and 330 ms for sounds), whereas for touch there is virtually no physical transmission, because tactile stimuli are presented directly at the body surface. On the other hand, the neural processing of visual information typically takes more time than the neural auditory processing (approximately 50 vs 10 ms, respectively) (Keetels & Vroomen, 2012). Both the differences in psychical and neural transmission time require the brain to be flexible on intersensory timing (Arnold, Johnston, & Nishida, 2005; King, 2005; Kopinska & Harris, 2004). The above-mentioned factors may lead to the physical asynchrony of multisensory signals, but surprisingly, perceptually our experiences are those of simultaneously presented multisensory events. Temporal coherence is thus maintained, despite the lags in arrival and processing time between the different senses (only in exceptional circumstances a single multisensory event is perceived as being separated, such as the thunder which is heard *after* the lightening). In order to maintain this temporal coherence, the brain has to deal with lags in arrival and processing time between the different senses. Psychophysical research has shown that experiences of synchronous events – and thus temporal coherence – may be accounted for by the existence of a 'temporal window of integration' and a 'temporal ventriloquism effect'.

Temporal window of integration

A hypothetical window of temporal integration might count as a compensatory mechanism for synchrony perception. Any information that falls within this window of temporal integration is potentially assigned to the same external events. Consequently, streams within the window are then treated as to have occurred simultaneously (Keetels & Vroomen, 2012) (see Figure 1A). Numerous studies have suggested the presence of a temporal window of MSI, or a range of interstimulus intervals over which multisensory stimuli are highly likely to be bound into a single perceptual event (Dixon & Spitz, 1980; Shams, Kamitani, & Shimojo, 2002; Van Wassenhove, Grant, & Poeppel, 2007). The boundaries of these temporal binding processes have been delineated by quantifying the perseverance and magnitude of multisensory effects (e.g., speeded motor reaction times, psychophysical illusions, reports of simultaneity) as the time interval between the presentation of the constituent multisensory stimuli is lengthened (Colonius & Diederich, 2004; Dixon & Spitz, 1980; Koppen & Spence, 2007; Munhall, Gribble, Sacco, & Ward, 1996; Shams et al., 2002; Van Wassenhove et al., 2007).

In an attempt to better understand synchrony perception, a number of researchers have focused on the 'behavior' of the temporal window by manipulating stimulus parameters (e.g., luminance of visual stimulus) and presenting different modalities (e.g., visual and auditory stimuli) and events (e.g., speech and musical events). Despite the differences in the type of stimuli, response tasks and statistical procedures used in these studies, three characteristics of the temporal window of integration (for mainly audiovisual stimuli) are relatively consistent across the majority of them (Vatakis, 2013). First, the temporal window for synchrony perception for audiovisual stimuli has a width on the order of several hundred milliseconds. A multisensory temporal window that is several hundred milliseconds wide is consistent with the estimation of the temporal window for multisensory enhancement and depression that has been reported in electrophysiological studies in animals (e.g., King & Palmer, 1985; Stein & Meredith, 1993). Second, the temporal window of synchrony is asymmetrical. The slope of the left side of the window is stepper, indicating that asynchrony is more readily detected for stimulus pairings when the auditory cue is presented first (Dixon & Spitz, 1980; McGurk & MacDonald, 1976; Powers, Hillock, & Wallace, 2009). Third, the width of the temporal window exhibits great variability across individuals, experimental setups and stimuli.

It is important to realize that the temporal window does not imply an active process. It refers to the interval in which no signal discrepancy is perceived and might therefore be seen as a more basic description rather than an explanation for how the brain maintains temporal coherence. In the next paragraph, we will discuss another phenomenon, known as 'temporal ventriloquism', as a potential compensatory mechanism for synchrony perception.

Temporal ventriloquism

Temporal ventriloquism is another mechanism of how the brain might deal with lags between the senses. The basic idea is that the perceived timing of a stimulus in one modality is actively shifted towards the other. For example, when a sound and a light are presented at slightly different onset times (usually in the order of approximately 100 ms), the perceived temporal asynchrony is typically reduced in such a way that the onset of the light is shifted towards the sound (see Figure 1B) (Morein-Zamir, Soto-Faraco, & Kingstone, 2003; Scheier, Nijhawan, & Shimojo, 1999; Stekelenburg & Vroomen, 2005; Vroomen & De Gelder, 2004; Vroomen & Keetels, 2006). The most cited explanation for this phenomenon is that there is a genuine crossmodal attraction of vision toward audition that is driven by a tendency of the brain to resolve any conflict between the senses about events that should normally yield converging data (for a review, see De Gelder & Bertelson, 2003; Vroomen & Keetels, 2010).

Scheier et al. (1999) were one of the first to demonstrate temporal ventriloquism by the use of a visual Temporal Order Judgment (TOJ) task. Participants were presented two lights, one above and one below a fixation point. The Stimulus Onset Asynchronies (SOAs) between these two lights varied between 60 ms 'upper light first' and 60 ms 'lower light first'. The participants' task was to judge which light came first, the upper or lower. To induce temporal ventriloquism, two sounds were added to the task, either presented before the first and after the second light (condition Auditory (A), Visual (V), Visual (V), Auditory (A)) AVVA) or in between the lights (condition VAAV). Results showed that participants were more sensitive to judge the temporal order of the lights (i.e., smaller intervals were still perceived correctly) in the AVVA condition compared to the VAAV condition. Due to temporal ventriloquism, the two sounds presumably attracted the temporal occurrence of the two lights, and thus effectively pulled the lights further apart in the AVVA condition (and closer together in the VAAV condition). The temporal resolutions of additional one-sound conditions, AVV or VVA, were not different from a visual-only baseline, suggesting that the effects were not due to the initial sound as a warning signal or some cognitive factor.

Further explorations by Morein-Zamir et al. (2003) on the temporal ventriloquism effect by Scheier et al. (1999) with sound-light intervals of 100 to 600 ms showed that the second sound induced temporal ventriloquism up to sound-light intervals of 200 ms. The first sound did not affect sensitivity to temporal order at all. Today, the effect of temporal ventriloquism has been shown in many other studies and paradigms (e.g., Fendrich & Corballis, 2001; Freeman & Driver, 2008; Stekelenburg & Vroomen, 2005; Vroomen & De Gelder, 2004; Vroomen & Keetels, 2006). All these demonstrations show that vision is flexible on the time dimension and that the perceived timing of a visual event is attracted towards other events in audition and touch, provided that the lag between them is less than 200 ms.

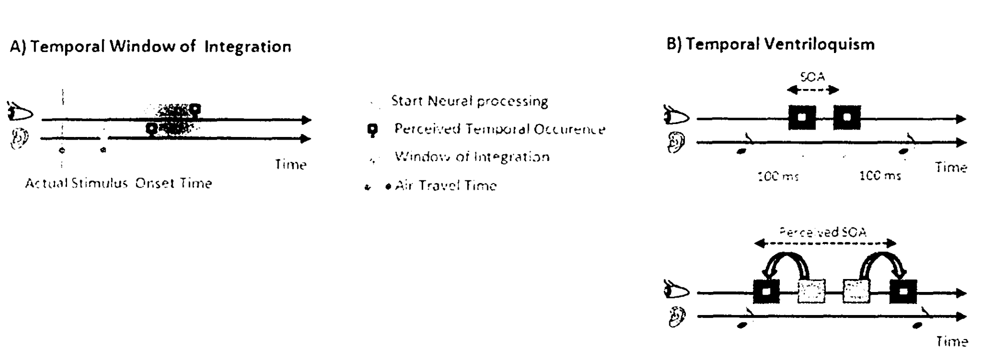


Figure 1. A schematic illustration of the hypothetical temporal window of integration (A; adapted from Keetels & Vroomen, 2011) and the temporal ventriloquism effect (B)

Temporal Order Judgment tasks

Both the width of the temporal window for MSI and temporal ventriloquism are measured by the use of a TOJ task or Simultaneity Judgment (SJ) task. In a typical TOJ task, stimuli are presented in different modalities at various SOAs and participants are asked to make judgments as to the order of stimulus presentation (e.g., Hirsh & Sherrick, 1961). For example, in an audiovisual TOJ task, participants may respond with 'sound first' or 'light first'. The data obtained from this task allow for the calculation of two measures, the Just Noticeable Difference (JND) and the Point of Subjective Simultaneity (PSS). The JND represents the smallest interval between two stimuli needed by participants to correctly judge which stimulus came first on 75% of the trials. A small JND thus reflects sensitivity to temporal order to be good, as smaller stimulus differences are required to correctly judge temporal order. Importantly, the temporal window of integration may vary with different stimuli. For example, for simple crossmodal stimuli like auditory tones and visual flashes, the JND has been found to be in order of approximately 25-50 ms (Zampini, Shore, & Spence, 2003) and JNDs of approximately 65 ms are reported for visual-tactile integration (Spence et al., 2001). The temporal window for more complex stimuli, like speech, shows a wider window of integration. For example, results of a study by Van Wassenhove et al. (2007) which focused on temporal coincidence in auditory visual speech perception, revealed temporal windows of maximal audiovisual integration of about 200 ms. The PSS provides an estimate of the time interval by which the stimulus in one sensory modality has to lead or lag the stimulus in the other modality in order for the two to be perceived as having been presented simultaneously. Although PSSs, like JNDs, differ between studies, the overall finding in auditory-visual studies is an asymmetry towards a visual lead stimulus (e.g., Lewald & Guski, 2003; Slutsky & Recanzone, 2001; Zampini, Guest, & Shore, 2005; Zampini et al., 2003). For perceiving temporal synchrony, lights thus have to be presented slightly before auditory inputs (which is in line with the longer neural processing time of visual stimuli compared to sounds (King & Palmer, 1985)). In a SJ task, stimuli are also presented at various SOAs, but rather than judging which stimulus came first, participants have to judge whether the stimuli were presented simultaneously or not.

TOJ tasks are frequently used to examine temporal ventriloquism and the sensitivity to temporal order of uni- or multisensory stimuli in 'healthy 'people. However, the use of TOJ tasks in clinical disorders like ASD and schizophrenia or learning disorders like dyslexia is far more limited (for an overview of TOJ tasks in the 'study groups', see Table 1). This is quite surprisingly, as consistent results of many different uni- and crossmodal studies in 'healthy 'people in the past have proven the strength of this behavioral task and its effectiveness. In addition, there are hardly any studies on the temporal ventriloquism effect as (possible) empirical evidence for intact or impaired low-level (audiovisual) integration in clinical or psychiatric patient groups as ASD and schizophrenia. These lacks in clinical research on MSI have been important considerations for the choices and set-ups of the studies in this thesis.

Table 1. An Overview of Temporal Order Judgment Studies in the 'Study Groups'

Study group	Author	Participants	Stimuli	Task	Results
ASD	Kwakye, Foss-Feig, Cascio, Stone, & Wallace, 2011	35 children with ASD and 27 TD controls	visual, auditory and visual with auditory cues	In the unimodal conditions, subjects have to judge which of the two circles (visual condition) or two clicks (auditory condition) came first. The audiovisual condition is as the visual-condition with sound stimuli (first sound synchronized with the first visual onset; second sound at audiovisual delays between 0-500 ms after the onset of the second circle). SOAs: via a staircase procedure.	No difference was found for thresholds on the visual TOJ task between the ASD and TD group, but thresholds were higher in ASD on the auditory task. On the multisensory TOJ task, children with ASD showed performance improvements over a wider range of temporal intervals than TD children, suggesting an extended temporal window of MSI in ASD.
ASD	Tommerdahl, Tannan, Holden, & Baranek, 2008	10 adults with ASD, 20 TD controls	vibrotactile	Vibrotactile stimuli are presented to the skin in an uniteral condition (same hand, digit 2 or 3) or bilateral condition (digit 2 of both hands). Subjects have to select the skin site that received the first stimulus. SOAs: via a staircase procedure.	Thresholds of the ASD subjects were higher for the unilateral TOJ, but comparable to the controls in the bilateral condition. Authors suggest a disruption of local functional connectivity in ASD, as the TOJ measure of subjects with ASD is not impacted by synchronizing stimuli.
Dyslexia	Jáskowski & Rusiak, 2008	16 dyslexic adolescents and 14 normal readers	visual	Participants judged the temporal order of the two visual stimuli, either presented vertically (top or down) or horizontally (left-right). SOAs: 0-188 ms or 0-178 ms.	The dyslexic readers performed generally worse than normal readers in both conditions, suggesting that dyslexic readers suffer from a more general problem of order discrimination.
Dyslexia	Hairston, Burdette, Flowers, Wood, & Wallace, 2005	36 dyslexic adults and 29 normal readers	visual with auditory cues	A visual TOJ task with sound conditions (first sound synchronized with the first visual onset; second sound at audiovisual delays between 0-350ms after the onset of the second circle). SOAs: via a staircase procedure.	Performance of the dyslexic readers differed significantly from the normal readers, specifically in that dyslexic readers integrated the auditory and visual information over longer temporal intervals.

Table 1. An Overview of Temporal Order Judgment Studies in the 'Study Groups' (continued)

Study group	Author	Participants	Stimuli	Task	Results
Dyslexia	Hari, Renvall, & Tanskanen, 2001	9 dyslexic adults and 14 normal readers	visual	Participants decided whether a visual bar in the left hemifield preceded or followed a similar bar on the right. SOAs: 0-210 ms.	The 'simultaneity window' of the dyslexic readers was significantly prolonged compared to the normal readers, indicating increased sluggishness of temporal processing. The performance of dyslexic readers showed preference for the right visual field.
Dyslexia	Liddle, Jackson, Rorden, & Jackson, 2009	experiment 1: 11 dyslexic adults and 16 normal readers experiment 2: 52 participants in total	visual	In exp. 1, participants judged the temporal order of two visual stimuli. In exp. 2, they had to indicate the shape of the stimulus that had appeared first (circle or triangle). SOAs: between 15-105 ms or 0-116 ms.	The dyslexic readers were significantly less sensitive to the temporal order of the visual stimuli.
Aging	Fiacconi, Harvey, Sekuler, & Bennett, 2013	experiment 1: 23 younger (M=22.1 yrs) and 21 older (M=73.9 yrs) adults experiment 2: 12 younger (M=25.5 yrs) and 12 older (M=75.2 yrs) adults	audiovisual	Participants judged whether the auditory or the visual stimulus was presented first in two experiments; the auditory and visual stimuli presented from the same and from a different location. SOAs: ± 0, 50, 100 or 250 ms.	In both experiments no evidence was found to suggest that audiovisual temporal order sensitivity declines with age.
Aging	Poliakoff, Shore, Lowe, & Spence, 2006	18 younger (M=21.8 yrs) and 18 older (M=74.2 yrs) adults	visual-vibrotactile	Pairs of visual and vibrotactile stimuli were presented to either hand and participants had to make temporal order judgments regarding which sensory modality appeared first. SOAs: via a staircase procedure.	Older participants required more time to accurately perceive the temporal order of the stimuli, suggesting that aging affects cross-modal temporal processing.

Table 1. An Overview of Temporal Order Judgment Studies in the 'Study Groups' (continued)

Study group	Author	Participants	Stimuli	Task	Results
Aging	Busey, Craig, Clark, & Humes, 2010	71 younger (18-30 yrs) 44 middle-aged (40-55 yrs) and 146 older (60-88 yrs) adults	visual	Participants performed on a series of visual TOJ tasks, in which they had the report to order of sequentially presented letters. SOAs: via a staircase procedure.	Performance differences were found between age groups on all measures of temporal processing and significant correlations with age were found for all measures.
Aging	Setti et al., 2011	18 younger (M=24 yrs) and 18 older (M=71 yrs) adults	audiovisual	Participants had to indicate which stimulus came first, visual or auditory. SOAs: 70 or 270 ms.	The older adults were less accurate than the younger adults in discriminating the temporal order at the 270 ms SOA. Based on the ERP data associated with this behavioral deficit the authors suggest that the ability to switch between sensory modalities may become less efficient with aging.
Aging	Virsu, Lahti-Nuuttila, & Laasonen, 2003	40 adults in different age groups (20-59 yrs old)	audiotactile, visuotactile and audiovisual	Participants judged which of two stimulus pulses was presented first (each pulse represented a different modality; tactile, auditory or visual). SOAs: via a staircase procedure.	Overall results showed a decline in temporal processing ability with age.

In this thesis, TOJ tasks will be used to allow us to address two questions, namely whether the 'study groups' have (1) diminished sensitivity to visual temporal order and (2) whether click sounds can improve their sensitivity to visual temporal order due to MSI in the form of temporal ventriloquism. If the 'study groups' suffer from impairments in MSI *per se*, they should have a *diminished* temporal ventriloquist effect because click sounds are not well-integrated with flashes. Alternatively, if their temporal resolution is abnormal, then sensitivity to visual temporal order will be impaired. In our dyslexia study, temporal ventriloquism was not examined; neither a TOJ task was used. In this study, we used the 'pip-and-pop' paradigm by Van der Burg et al. (2008) to examine whether the presence of sounds could improve visual search time in individuals with dyslexia. One of the reasons for this different approach was, as visible in Table 1, the already more present study results of dyslexic reader's performances on (audio)visual TOJ tasks.

Autism

What is autism?

Autism Spectrum Disorders (ASD) are characterized by deficits in social interactions, communication, and by restricted interests and/or repetitive behaviors (APA, 1994). In the Diagnostic and Statistical Manual of Mental Disorder-IV (DSM-IV), autism is the most severe of the Pervasive Developmental Disorders (PDD), which include also milder forms such as Asperger's syndrome and Pervasive Developmental Disorders, Not Otherwise Specified (PDD-NOS). Within a diagnosis of autism, there can be a wide range of intellectual ability. There also exists considerable phenotypic variation involving the pace of language development, the presence of epilepsy, and the range of cognitive ability (Marco, Hinkley, Hill, & Nagarajan, 2011). There are many known etologies that contribute to an ASD phenotype, including genetic variation (e.g., fragile X and tuberous sclerosis), environmental exposures (e.g., in utero valproic acid exposure) and prematurity. In the absence of 'clear' biological markers, the diagnosis of ASD is typically determined by clinicians using behavioral assessments, such as the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 1989) and the Autism Diagnostic Interview Revised (ADI-R; Lord, Rutter, & Le Couteur, 1994).

In addition to the more 'well-known' impairments in communication and social behavior, atypical behavioral responses to sensory information are also often reported in persons with ASD. Indeed, early clinical observations of atypical reactions to sensory stimuli date back to Kanner (1943). A study by Dahlgren and Gillberg (1989) showed that parents of infants with autism already often reported sensory peculiarities early in the development of their infants. For example, children and adults with autism are reported to be easily distressed or preoccupied by innocuous sights, sounds, odors and textures, and are not responsive to other more meaningful sensations such as the sound of their names (Baranek, 1999; Talay-Ongan & Wood, 2000; Waterhouse, 1999). Atypical sensory-perceptual behaviors appear to persist throughout the development of individuals with autism (Greenspan & Weider, 1997; O'Neill & Jones, 1997).

Autism and MSI

Based on the leading theories of autism, the abnormalities in sensory processing may eventually involve multisensory processing and integration. The last decade, empirical evidence of multisensory processing in ASD is growing and there are now several clinical and anecdotal reports that suggest that the sensory abnormalities which are observed among individuals with ASD involve more than one sensory modality (Iarocci & McDonald, 2006). Many research on ASD focused on the processing of audiovisual social stimuli related to communication, such as speech sounds accompanied by their requisite lip movements and the MSI of emotions as perceived from the face and the voice. A majority of these studies suggests that people with ASD have problems with audiovisual integration of social and emotional stimuli that could account for the atypical social behavior of individuals with ASD (Bebko, Weiss, Demark, & Gomez, 2006; De Gelder, Vroomen, & Van der Heide, 1991; Magnée, De Gelder, Van Engeland, & Kemner, 2008; Mongillo et al., 2008; Russo et al., 2010; Smith & Bennetto, 2007; Taylor, Isaac, & Milne, 2010).

Research on MSI of lower-level, non-social stimuli in ASD is more scarce, but a majority of these studies found audiovisual integration in ASD to be intact (Foss-Feig et al., 2010; Grossman, Schneps, & Tager-Flusberg, 2009; Keane, Rosenthal, Chun, & Shams, 2010; Kwakye et al., 2011; Magnée, Oranje, Van Engeland, Kahn, & Kemner, 2009; Mongillo et al., 2008; Van der Smagt, Van Engeland, & Kemner, 2007). For example, Mongillo et al. (2008) compared the results of a group of children with and without ASD on six perceptual tasks designed to characterize the nature of the audiovisual processing difficulties experience by children with ASD. They found that children with ASD score significantly lower than children without ASD on AV tasks involving human faces and voices, but scored similarly on audiovisual tasks involving non-human stimuli (bouncing balls). Comparing the results of the different ASD studies, there seems to be a dichotomy between the processing of complex and lower-level stimuli.

Finally, there are some recent, but limited studies on temporal processing in ASD which report differences in various aspects of temporal functioning (e.g., Bebko et al., 2006; Szelag, Kowalska, Galkowski, & Pöppel, 2004). Studies by Kwakye et al. (2011) and Foss-Feig et al. (2010), for example, proposed that individuals with ASD may have an extended window of multisensory temporal binding. Kwakye et al. (2011) compared TD children and children with ASD on TOJ tasks with visual, auditory, and audiovisual stimuli and reported no differences in sensitivity for visual temporal order between the two groups. Thresholds on the auditory TOJ task, though, were higher in children with ASD. In the multisensory TOJ task, the authors relied on the phenomenon known as temporal ventriloquism (Scheier et al., 1999), where click sounds can improve sensitivity for visual temporal order if the clicks are presented within a certain time window. Children with ASD showed performance improvements over a wider range of temporal intervals than TD children, thus reinforcing the idea that children with ASD have a wider temporal window of MSI.

Schizophrenia

What is schizophrenia?

Schizophrenia is a serious mental illness characterized by incoherent or illogical thoughts, bizarre behavior and speech, and delusions or hallucinations, such as hearing voices (APA, 1994). Schizophrenia typically begins in early adulthood and commonly has a chronic course albeit with fluctuating patterns and cognitive disability. Severe mood symptoms up to and including manic and major depressive episodes, are present in many cases (Gejman, Sanders, & Duan, 2010). Schizophrenia belongs to a group of pathologies known as complex genetic disorders and it has traditionally been assumed that changes in DNA sequence are solely responsible for the transmission of schizophrenia. More recent epidemiological studies strongly suggest that environmental risk factors are also involved, including various obstetric complications (Byrne, Agerbo, Bennedsen, Eaton, & Mortensen, 2007; Mittal, Ellman, & Cannon, 2008) urban birth or residence, famines, migrant status, and seasonal effects (via prenatal infections, e.g., influenza; McGrath, Saha, Chant, & Welham, 2008). There are no diagnostic laboratory tests for schizophrenia. Instead, the diagnosis relies on clinical observation and self-reports.

In contemporary research on schizophrenia, there is growing evidence that schizophrenia may be associated with a fundamental disturbance in the temporal coordination of information processing in the brain, leading to dysfunctions in the timing of perceptual, cognitive and motor processes, and the disturbances of consciousness (e.g., Andreasen, Paradiso, & O'Leary, 1998; Bressler, 2003; Carroll, Boggs, O'Donnell, Shekhar, & Hetrick, 2008; Carroll, O'Donnell, Shekhar, & Hetrick, 2009; Phillips & Silverstein, 2003). Accordingly, classic symptoms of schizophrenia such as thought disorder and disorganized and contextually inappropriate behavior may be manifestations of a timing dysfunction (Carroll et al., 2008). There is also growing evidence that individuals with schizophrenia exhibit processing abnormalities at both the behavioral and neural level in a number of sensory modalities (e.g., Ford et al., 2004; Light et al., 2006; Williams, Light, Braff, & Ramachandran, 2010), which could lead to impaired MSI in individuals with schizophrenia.

Schizophrenia and MSI

Although cognitive dysfunction is considered a hallmark feature of schizophrenia, evidence suggests that disturbances in basic sensory processing may underlie many of the cognitive impairments observed (Javitt, 2009). While deficits in auditory and visual processing are often observed in schizophrenia, relatively little is known about how MSI is affected by the disorder. Comparable to ASD research, most studies on MSI in schizophrenia examined the integration of audiovisual information of speech (De Gelder, Vroomen, Annen, Masthof, & Hodiamont, 2002; Pearl et al., 2009; Ross et al., 2007; Szycik et al., 2009) and the audiovisual processing of emotional stimuli (e.g., Castagna et al., 2013; De Gelder et al., 2005; De Jong, Hodiamont, Van den Stock, & De Gelder, 2009; Van den Stock, de Jong, Hodiamont, & De Gelder, 2011). Overall consensus is that higher-order audiovisual integration is likely impaired in individuals with schizophrenia.

There is less agreement about integration deficits at more basic levels with lower-level stimuli in people with schizophrenia. For example, an electroencephalogram (EEG) study by Stekelenburg, Maes, Van Gool, Sitskoorn & Vroomen (in press) reported that in non-psychiatric controls visual information that predicts the onset of a sound (as in the video of a handclap) reduces the auditory-evoked N1 when compared to the N1 elicited in an auditory-only condition. This reduction of the N1 was absent in patients with schizophrenia, suggesting a deficit in audiovisual temporal prediction of sound. Similar results of impaired MSI in individuals with schizophrenia were also found by William et al. (2010) and Magneé et al. (2009). However, other studies found opposite findings, as their results showed intact MSI in schizophrenia individuals (De Gelder et al., 2002; Foucher, Lacambre, Pham, Giersch, & Elliott, 2007; Peled, Ritsner, Hirschmann, Geva, & Modai, 2000; Stone et al., 2011).

It has been suggested that schizophrenia may be associated with a fundamental disturbance in the temporal coordination of information processing in the brain. Some studies on timing and temporal processing provide evidence for a deficit in temporal auditory precision (Carroll et al., 2008), more general time perception abnormalities (e.g., Carroll et al., 2009; Lee et al., 2009) and poor temporal coordination of cognitive and perceptual processing (Bolbecker et al., 2009). Foucher et al. (2007) suggested that individuals with schizophrenia sometimes display more MSI than controls, because the time at which they perceive two stimuli as simultaneous, their 'window of simultaneity', is lengthened. Evidence of this 'lengthened window of integration' in schizophrenia was also found by a recent study by Parsons et al. (2013).

Developmental dyslexia

What is developmental dyslexia?

Developmental dyslexia (DD) is a neurobiological disorder characterized by a difficulty in reading acquisition despite adequate intelligence, conventional education, and motivation (APA, 1994). Children with dyslexia present deficits in phonological processing, i.e., the awareness of the sound structure of words, but also show slow lexical retrieval and poor phonological short-term memory (see Ramus, 2003, for a review). As reading ability is correlated with intelligence, dyslexia is typically diagnosed using discrepancy scores (APA, 1994), which measure the difference between the actual reading performance and the reading performance predicted on the basis of the person's intelligence (Skottun & Skoyles, 2006). Because the cognitive phenotype varies so widely across subjects, one is tempted to search for a core mechanism uniting this diversity of disorders. There are, however, various hypotheses concerning the possible origin of dyslexia, for example deficits in auditory processing (e.g., Nagarajan et al., 1999) and a deficit in temporal processing (Farmer & Klein, 1995; Habib, 2000). The prevailing view supports the *hypothesis that dyslexia results from a specific deficit* of auditory-phonological perception, representation, and phonological memory (see Vellutino, Fletcher, Snowling, & Scanlon, 2004; Ziegler & Goswami, 2005, for reviews).

Apart from their phonological difficulties, people with dyslexia often suffer from a variety of subtle sensory and motor deficits. Whether these deficits have any causal relation to the reading disorder, or are totally independent, is currently under debate. Stein (2003) suggests that a magnocellular deficiency causes a type of visual attention deficit in dyslexia, which has made it important to assess visual attention in dyslexic readers. A more recent hypothesis that links the magnocellular deficit with reading problems is that dyslexics may have 'Sluggish Attentional Shifting' (SAS; Hari & Renvall, 2001). The basic notion underlying SAS is that sensory input is chunked, and that attention of dyslexic subjects, once engaged on a chunk, cannot be easily disengaged (Hari & Renvall, 2001). In addition, there is also convincing empirical evidence for temporal processing deficits in many disabled readers, especially in people with dyslexia (for a review, see Farmer & Klein, 1995). Temporal processing deficits were also found in the visual modality (DiLollo, Hanson, & McIntyre, 1983; May, Williams, & Dunlap, 1988).

Developmental dyslexia and MSI

Most studies on dyslexia focus on the more prevailing hypotheses of dyslexia, like visual deficits or a specific deficit of auditory-phonological perception, representation, and phonological memory. Only little evidence is gathered to directly address the capacity of dyslexics to integrate information between the different senses. However, MSI is undoubtedly a critical process in the development of linguistic skills (especially reading), given that such skills are vitally dependent on the rapid and accurate association between the appropriate auditory and visual language elements (Massaro, Cohen, & Smeele, 1996; Tallal, Miller, & Fitch, 1993). A fMRI study by Blau, Van Atteveldt, Ekkebus, Goebel, & Blomert (2009) investigated the neural processing of letters and speech sounds in unisensory (visual and auditory) and multisensory (audiovisual congruent and audiovisual incongruent) conditions as a function of reading ability. Their data revealed reduced audiovisual integration in adult dyslexic readers, which is, according to the authors, directly associated with a more fundamental deficit in auditory processing of speech sounds. The authors suggest that the data provide a neurofunctional account of developmental dyslexia, in which phonological processing deficits are linked to reading failure through a deficit in neural integration of letters and speech sounds (i.e., audiovisual information). Another study by Hairston, Burdette, Flowers, Wood, & Wallace (2005), which examined the effects of task-irrelevant auditory information on the performance of a visual TOJ task, showed that dyslexic subjects' performance differed significantly from that of the control group. Specifically, the dyslexic readers integrated the auditory and visual information over longer temporal intervals. These results support the hypothesis of altered crossmodal temporal processing in dyslexia, as it showed an extended temporal window for binding visual and auditory cues. In the past, various authors argued that dyslexics exhibit deficits in different sensory systems which involve alterations in temporal information processing (e.g., Kinsbourne, Rufo, Gamzu, Palmer, & Berliner, 1991; Laasonen, Service, & Virsu, 2002; Tallal, 1980)

Developmental aspects of MSI

Besides impairments in MSI due to psychiatric or neurbiological disorders, MSI seems to be subject to developmental changes during typical developmental life hood. Several developmental studies have highlighted that significant changes take place in multisensory temporal processing as maturation progresses (e.g., Lewkowicz, 1996; Lewkowicz & Ghazanfar, 2006; Lewkowicz, Sowinski, & Place, 2008). For example, Lewkowicz (1996) showed that when compared to adults, infants have a larger temporal window for binding asynchronous visual and auditory stimuli, suggesting that they perceptually fuse temporally disparate multisensory pairs that are not fused in adults. A recent study by Hillock, Powers & Wallace (2011) compared the ability of 10- and 11-year-olds and adults to detect audiovisual temporal asynchrony. Their findings revealed striking and asymmetric age-related differences, as children were able to identify asynchrony as readily as adults when visual stimuli preceded auditory cues, but significant group difference were found at moderately long stimulus onset asynchronies where the auditory stimulus was first. These results suggest that changes in audiovisual temporal perception extend beyond the first decade of life. In a follow-up study, Hillock-Dunn and Wallace (2012) again reported changes in audiovisual temporal processing from early childhood through early adulthood, providing compelling evidence that differences in the perception of multisensory temporal relations persist well into adolescence. It thus seems that multisensory processing continues to develop into adolescence, suggesting that multisensory processing has a more protracted developmental trajectory than the unisensory systems.

In addition, as we age, there are significant changes in all sensory systems and a variety of cognitive functions, like increased hearing thresholds (Liu & Yan, 2007) and declines in motor speed, executive function and memory (Birren & Fisher, 1995; Rhodes, 2004). There are also widespread changes in the aging brain, for example, alterations in neurotransmitter systems (Bäckman, Nyberg, Lindenberger, Li, & Farde, 2006) and altered patterns of functional activity during cognitive tasks (Cabeza et al., 2004; Grady, 2008). General consensus is that there is indeed deterioration of sensory processes in the elderly (e.g., Corso, 1971; Craig, Rhodes, Busey, Kewley-Port, & Humes, 2010; Habak & Faubert, 2000; Keller, Morton, Thomas, & Potter, 1999; Nusbaum, 1999; Weiss, 1963) which could eventually lead to deficits in MSI. However, there is some debate going on about intact versus impaired MSI in elderly people. For example, a magnetoencephalography (MEG) study by Stephen, Knoefel, Adair, Hart & Aine (2010), reported suppressed cortical MSI response in the elderly, which corresponds with slower reaction times (RTs) and reduced RT facilitation. The authors suggested that this may be related to poor cortical integration based on timing changes in unisensory processing in the elderly. Interestingly, on the other hand a number of studies that focused on MSI in the elderly has demonstrated that MSI in older adults is actually enhanced (Diaconescu, Hasher, & McIntosh, 2013; Diederich, Colonius, & Schomburg, 2008; Laurienti, Burdette, Maldjian, & Wallace, 2006; *Mahoney, Verghese, Dumas, Wang, & Holtzer, 2012;* Peiffer, Mozolic, Hugenschmidt, & Laurienti, 2007).

In sum, there seems to be consensus that MSI is subject to maturation progresses, but more evidence would be needed to create a developmental trajectory of normative multisensory temporal processing.

Summary of this thesis

The central research aim in this thesis is to increase our understanding of low-level audiovisual integration in people with ASD, schizophrenia, dyslexia and in the elderly and to relate possible impairments to clinical features of the disorders. For this purpose, different behavioral tasks were used. We compared our research findings of each clinical group with a group of typically developing (TD) individuals matched on age, gender and IQ.

In **Chapter 2**, we examined visual temporal processing and audiovisual integration in individuals with schizophrenia using a visual TOJ task. Participants had to judge the temporal order of visual stimuli and we used the illusion of 'temporal ventriloquism' to investigate whether the presence of click sounds improved their performance on this task. The results showed that, compared to a non-psychiatric control group, people with schizophrenia were less sensitive in their judgment of the temporal order of the visual stimuli. However, their sensitivity to visual temporal order improved at an equal amount as in the control group when two accessory click sounds were added to the task (temporal ventriloquism).

In **Chapter 3**, we examined sensitivity of audiovisual temporal order in high-functioning adolescents with ASD to answer a critical question whether people with ASD suffer from intersensory temporal deficits that may underlie other impairments in MSI. Therefore, we used an audiovisual TOJ task with three kinds of stimuli that differ on a number of potentially relevant dimensions: a flash/beep, a video of a handclap with the corresponding sound, and a video of a face articulating a syllable with the corresponding speech sound. The asynchrony between the audio and video was varied and participants had to judge whether the auditory stimulus came 'early' or 'late' with respect to the video. By using these different stimuli we varied the complexity of the stimuli that allowed us to examine whether people with ASD suffer from a general or more specific impairment in audiovisual temporal processing. Results showed that the adolescents with ASD were generally less sensitive in their judgments of audiovisual temporal order (larger JNDs), suggesting that they suffer from a more general impairment of audiovisual temporal processing.

In **Chapter 4** we took a closer look on visual processing in high-functioning adolescents with ASD and we investigated whether abrupt click sounds could improve the visual processing of flashes in individuals with ASD in a same beneficial way as it does in healthy controls. We used three tasks: (1) a task where click sounds improve sensitivity for visual temporal order (temporal ventriloquism); (2) a task where a click sound improves visual search ('pip-and-pop'), and (3) a task where a click sound speeds up the visual orienting to a peripheral target (clock reading). We found that adolescents with ASD, compared to TD adolescents, show diminished sensitivity to visual temporal order, without problems in the shifting and/or disengagement of visual attention. In all tasks visual performance of the ASD group improved by the presence of click sounds by at least equal amounts as in the TD group.

In **Chapter 5** we examined whether sounds could improve visual search time in individuals with developmental dyslexia. We hypothesized that if people with dyslexia suffer from 'Sluggish Attentional Shifting' (Hari & Renvall, 2001), they may profit from a transient sound because of a general alerting effect that improves the disengagement of attention. We measured the shifting of attention of dyslexia readers in a visual search task with dynamic cluttered displays (Van der Burg et al., 2008). Results showed that people with dyslexia were generally slower than normal readers in searching horizontal or vertical targets among oblique distracters, but the addition of a click sound presented in synchrony with a color change of the target drastically improved their performance up to the level of the normal readers.

In **Chapter 6** we used five age groups (between 20-70 years old) to trace the development of sensitivity for temporal order in the auditory, visual, and crossmodal (audiovisual) domain using standard visual, auditory, and audiovisual TOJ tasks. We also obtained a measure of MSI using temporal ventriloquism, to address the question whether temporal ventriloquism effect varies with age. Our findings showed that older adults are less sensitive to the temporal order of visual, auditory, and audiovisual stimuli compared to younger adults. However, elder persons showed enhanced MSI to low-level audiovisual stimuli.

Chapter 7 contains a summary and discussion of the main findings. Furthermore, methodological considerations, implications for future research and clinical implications are described.

References

Andreasen, N. C., Paradiso, S., & O'Leary, D. S. (1998). 'Cognitive dysmetria' as an integrative theory of schizophrenia: A dysfunction in cortical subcortical-cerebellar circuitry? *Schizophrenia Bulletin, 24*(2), 203-218.

APA (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington DC: American Psychiatric Association.

Arnold, D. H., Johnston, A., & Nishida, S. (2005). Timing sight and sound. *Vision Res, 45*(10), 1275-1284.

Baranek, G. T. (1999). Autism during infancy: A retrospective video analysis of sensory-motor and social behaviors at 9-12 months of age. *Journal of Autism and Developmental Disorders, 29*(3), 213-224.

Bebko, J. M., Weiss, J. A., Demark, J. L., & Gomez, P. (2006). Discrimination of temporal synchrony in intermodal events by children with autism and children with developmental disabilities without autism. *Journal of Child Psychology and Psychiatry, 47*(1), 88-98.

Bertone, A., Mottron, L., Jelenic, P., & Faubert, J. (2005). Enhanced and diminished visuo-spatial information processing in autism depends on stimulus complexity. *Brain, 128*, 2430-2441.

Birren, J. E., & Fisher, L. M. (1995). Aging and speed of behavior: Possible consequences for psychological functioning. *Annu Rev Psychol, 46*, 329-353.

Blau, V., Van Atteveldt, N., Ekkebus, M., Goebel, R., & Blomert, L. (2009). Reduced neural integration of letters and speech sounds links phonological and reading deficits in adult dyslexia. *Current Biology, 19*(6), 503-508.

Bolbecker, A. R., Mehta, C. S., Edwards, C. R., Steinmetz, J. E., O'Donnell, B. F., & Hetrick, W. P. (2009). Eye-blink conditioning deficits indicate temporal processing abnormalities in schizophrenia. *Schizophr Res, 111*(1-3), 182-191.

Bressler, S. L. (2003). Cortical coordination dynamics and the disorganization syndrome in schizophrenia. *Neuropsychopharmacology, 28*, S35-S39.

Busey, T., Craig, J., Clark, C., & Humes, L. (2010). Age-related changes in visual temporal order judgment performance: Relation to sensory and cognitive capacities. *Vision Research, 50*(17), 1628-1640.

Byrne, M., Agerbo, E., Bennedsen, B., Eaton, W. W., & Mortensen, P. B. (2007). Obstetric conditions and risk of first admission with schizophrenia: A Danish national register based study. *Schizophr Res, 97*(1-3), 51-59.

Bäckman, L., Nyberg, L., Lindenberger, U., Li, S. C., & Farde, L. (2006). The correlative triad among aging, dopamine, and cognition: Current status and future prospects. *Neurosci Biobehav Rev, 30*(6), 791-807.

Cabeza, R., Daselaar, S. M., Dolcos, F., Prince, S. E., Budde, M., & Nyberg, L. (2004). Task-independent and task-specific age effects on brain activity during working memory, visual attention and episodic retrieval. *Cereb Cortex, 14*(4), 364-375.

Carroll, C. A., Boggs, J., O'Donnell, B. F., Shekhar, A., & Hetrick, W. P. (2008). Temporal processing dysfunction in schizophrenia. *Brain Cogn, 67*(2), 150-161. doi: 10.1016/j.bandc.2007.12.005

Carroll, C. A., O'Donnell, B. F., Shekhar, A., & Hetrick, W. P. (2009). Timing dysfunctions in schizophrenia span from millisecond to several-second durations. *Brain Cogn, 70*(2), 181-190.

Castagna, F., Montemagni, C., Maria Milani, A., Rocca, G., Rocca, P., Casacchia, M., & Bogetto, F. (2013). Prosody recognition and audiovisual emotion matching in schizophrenia: The contribution of cognition and psychopathology. *Psychiatry Res, 205*(3), 192-198.

Colonius, H., & Diederich, A. (2004). Multisensory interaction in saccadic reaction time: A time-window-of-integration model. *J Cogn Neurosci, 16*(6), 1000-1009.

Corso, J. F. (1971). Sensory processes and age effects in normal adults. *J Gerontol, 26*(1), 90-105.

Craig, J. C., Rhodes, R. P., Busey, T. A., Kewley-Port, D., & Humes, L. E. (2010). Aging and tactile temporal order. *Atten Percept Psychophys, 72*(1), 226-235.

Dahlgren, S. O., & Gillberg, C. (1989). Symptoms in the 1st 2 years of life - a preliminary population study of infantile-autism. *European Archives of Psychiatry and Clinical Neuroscience, 238*(3), 169-174.

De Gelder, B., & Bertelson, P. (2003). Multisensory integration, perception and ecological validity. *Trends Cogn Sci, 7*(10), 460-467.

De Gelder, B., Vroomen, J., Annen, L., Masthof, E., & Hodiamont, P. P. G. (2002). Audio-visual integration in schizophrenia. *Schizophrenia Research, 59*, 211-218.

De Gelder, B., Vroomen, J., De Jong, S. J., Masthof, E. D., Trompenaars, F. J., & Hodiamont, P. P. G. (2005). Multisensory integration of emotional faces and voices in schizophrenics. *Schizophrenia Research, 72*, 195-203.

De Gelder, B., Vroomen, J., & Van der Heide, L. (1991). Face recognition and lip-reading in autism. *European Journal of Cognitive Psychology, 3*(69-86).

De Jong, J. J., Hodiamont, P. P. G., Van den Stock, J., & De Gelder, B. (2009). Audiovisual emotion recognition in schizophrenia: Reduced integration of facial and vocal affect. *Schizophrenia Research, 107*, 286-293.

Diaconescu, A. O., Hasher, L., & McIntosh, A. R. (2013). Visual dominance and multisensory integration changes with age. *Neuroimage, 65*, 152-166.

Diederich, A., Colonius, H., & Schomburg, A. (2008). Assessing age-related multisensory enhancement with the time-window-of-integration model. *Neuropsychologia, 46*(10), 2556-2562.

DiLollo, V., Hanson, D., & McIntyre, J. S. (1983). Initiatal stages of visual information processing in dyslexia. *Journal of Experimental Psychology: Human Perception and Performance, 9*, 923-935.

Dixon, N. F., & Spitz, L. (1980). The detection of auditory visual desynchrony. *Perception, 9*(6), 719-721.

Farmer, M. E., & Klein, R. M. (1995). The evidence for a temporal processing deficit linked to dyslexia: A Review. *Psychonomic Bulletin & Review, 2*(4), 460-493.

Fendrich, R., & Corballis, P. M. (2001). The temporal cross-capture of audition and vision. *Percept Psychophys, 63*(4), 719-725.

Fiacconi, C. M., Harvey, E. C., Sekuler, A. B., & Bennett, P. J. (2013). The influence of aging on audiovisual temporal order judgments. *Experimental Aging Research, 39*(2), 179-193.

Ford, J. M., Gray, M., Whitfield, S. L., Turken, A. U., Glover, G., Faustman, W. O., & Mathalon, D. H. (2004). Acquiring and inhibiting prepotent responses in schizophrenia - Event-related brain potentials and functional magnetic resonance imaging. *Archives of General Psychiatry, 61*(2), 119-129.

Foss-Feig, J. H., Kwakye, L. D., Cascio, C. J., Burnette, C. P., Kadivar, H., Stone, W. L., & Wallace, M. T. (2010). An extended multisensory temporal binding window in autism spectrum disorders. *Experimental Brain Research, 203*(2), 381-389.

Foucher, J. R., Lacambre, M., Pham, B.-T., Giersch, A., & Elliott, M. A. (2007). Low time resolution in schizophrenia. Lengthened windows of simultaneity for visual, auditory and bimodal stimuli. *Schizophrenia Research, 97*, 118-127.

Foxe, J. J., & Molholm, S. (2009). Ten years at the multisensory forum: Musings on the evolution of a field. *Brain Topography, 21*, 149-154.

Freeman, E., & Driver, J. (2008). Direction of visual apparent motion driven solely by timing of a static sound. *Curr Biol, 18*(16), 1262-1266.

Gejman, P. V., Sanders, A. R., & Duan, J. (2010). The role of genetics in the etiology of schizophrenia. *Psychiatr Clin North Am, 33*(1), 35-66.

Grady, C. L. (2008). Cognitive neuroscience of aging. *Ann N Y Acad Sci, 1124*, 127-144.

Greenspan, S., & Weider, S. (1997). Developmental patterns and outcomes in infants and children with disorders in relating and communicating. A chart review of 200 cases of children with autistic spectrum diagnoses. *Journal of Developmental and Learning Disorders, 1*, 87-141.

Grossman, R. B., Schneps, M. H., & Tager-Flusberg, H. (2009). Slipped lips: Onset asynchrony detection of auditory-visual language in autism. *Journal of Child Psychology and Psychiatry, 50*(4), 491-497.

Habak, C., & Faubert, J. (2000). Larger effect of aging on the perception of higher-order stimuli. *Vision Research, 40*(8), 943-950.

Habib, M. (2000). The neurological basis of developmental dyslexia - An overview and working hypothesis. *Brain, 123*, 2373-2399.

Hairston, W. D., Burdette, J. H., Flowers, D. L., Wood, F. B., & Wallace, M. T. (2005). Altered temporal profile of visual-auditory multisensory interactions in dyslexia. *Experimental Brain Research, 166*(3-4), 474-480.

Hari, R., & Renvall, H. (2001). Impaired processing of rapid stimulus sequences in dyslexia. *Trends in Cognitive Sciences, 5*(12), 525-532.

Hari, R., Renvall, H., & Tanskanen, T. (2001). Left minineglect in dyslexic adults. *Brain, 124*, 1373-1380.

Hillock, A. R., Powers, A. R., & Wallace, M. T. (2011). Binding of sights and sounds: Age-related changes in multisensory temporal processing. *Neuropsychologia, 49*(3), 461-467.

Hillock-Dunn, A., & Wallace, M. T. (2012). Developmental changes in the multisensory temporal binding window persist into adolescence. *Developmental Science, 15*(5), 688-696.

Hirsh, I. J., & Sherrick, C. E. (1961). Perceived order in different sense modalities. *J Exp Psychol, 62*, 423-432.

Iarocci, G., & McDonald, J. (2006). Sensory integration and the perceptual experience of persons with Autism. *Journal of Autism and Developmental Disorders, 36*(1), 77-89.

Javitt, D. C. (2009). When doors of perception close: Bottom-up models of disrupted cognition in schizophrenia. *Annu Rev Clin Psychol, 5*, 249-275.

Jáskowski, P., & Rusiak, P. (2008). Temporal order judgment in dyslexia. *Psychological research, 72*, 65-73.

Kanner, L. (1943). Autistic disturbances of affective content. *Nervous Child, 2*, 217-250.

Keane, B. P., Rosenthal, O., Chun, N. H., & Shams, L. (2010). Audiovisual integration in high functioning adults with autism. *Research in Autism Spectrum Disorders, 4*(2), 276-289.

Keetels, M., & Vroomen, J. (2012). Perception of synchrony between the senses. In M. M. Murray & M. T. Wallace (Eds.), *Frontiers in the neural basis of multisensory processes* (pp. 147-177). London: Taylor & Francis Group.

Keller, B. K., Morton, J. L., Thomas, V. S., & Potter, J. F. (1999). The effect of visual and hearing impairments on functional status. *Journal of the American Geriatrics Society, 47*(11), 1319-1325.

Kerkhoff, G. (1999). Multimodal spatial orientation deficits in left-sided visual neglect. *Neuropsychologia, 37*(12), 1387-1405.

Kerkhoff, G., Artinger, F., & Ziegler, W. (1999). Contrasting spatial hearing deficits in hemianopia and spatial neglect. *Neuroreport, 10*(17), 3555-3560.

King, A. J. (2005). Multisensory integration: Strategies for synchronization. *Curr Biol, 15*(9), R339-341.

King, A. J., & Palmer, A. R. (1985). Integration of visual and auditory information in bimodal neurones in the guinea-pig superior colliculus. *Exp Brain Res, 60*(3), 492-500.

Kinsbourne, M., Rufo, D. T., Gamzu, E., Palmer, R. L., & Berliner, A. K. (1991). Neuropsychological deficits in adults with dyslexia. *Developmental Medicine and Child Neurology, 33*(9), 763-775.

Kopinska, A., & Harris, L. R. (2004). Simultaneity constancy. *Perception, 33*(9), 1049-1060.

Koppen, C., & Spence, C. (2007). Audiovisual asynchrony modulates the Colavita visual dominance effect. *Brain Res, 1186*, 224-232.

Kwakye, L. D., Foss-Feig, J. H., Cascio, C. J., Stone, W. L., & Wallace, M. T. (2011). Altered auditory and multisensory temporal processing in autism spectrum disorders. *Frontiers in integrative neuroscience, 4*, 129.

Laasonen, M., Service, E., & Virsu, V. (2002). Crossmodal temporal order and processing acuity in developmentally dyslexic young adults. *Brain and Language, 80*(3), 340-354.

Laurienti, P. J., Burdette, J. H., Maldjian, J. A., & Wallace, M. T. (2006). Enhanced multisensory integartion in older adults. *Neurobiology of aging, 27*, 1155-1163.

Lee, K.-H., Bhaker, R. S., Mysore, A., Parks, R. W., Birkett, P. B. L., & Woodruff, P. W. R. (2009). Time perception and its neuropsychological correlates in patients with schizophrenia and in healthy volunteers. *Psychiatry Research, 166*, 174-183.

Lewald, J., & Guski, R. (2003). Crossmodal perceptual integration of spatially and temporally disparate auditory and visual stimuli. *Brain Res Cogn Brain Res, 16*(3), 468-478.

Lewkowicz, D. J. (1996). Perception of auditory-visual temporal synchrony in human infants. *J Exp Psychol Hum Percept Perform, 22*(5), 1094-1106.

Lewkowicz, D. J., & Ghazanfar, A. A. (2006). The decline of cross-species intersensory perception in human infants. *Proc Natl Acad Sci U S A, 103*(17), 6771-6774.

Lewkowicz, D. J., Sowinski, R., & Place, S. (2008). The decline of cross-species intersensory perception in human infants: Underlying mechanisms and its developmental persistence. *Brain Res, 1242*, 291-302.

Liddle, E. B., Jackson, G. M., Rorden, C., & Jackson, S. R. (2009). Lateralized temporal order judgement in dyslexia. *Neuropsychologia, 47*(14), 3244-3254.

Light, G. A., Hsu, J. L., Hsieh, M. H., Meyer-Gomes, K., Sprock, J., Swerdlow, N. R., & Braff, D. L. (2006). Gamma band oscillations reveal neural network cortical coherence dysfunction in schizophrenia patients. *Biological Psychiatry, 60*(11), 1231-1240. doi: 10.1016/j.biopsych.2006.03.055

Liu, X. Z., & Yan, D. (2007). Ageing and hearing loss. *J Pathol, 211*(2), 188-197. doi: 10.1002/path.2102

Lord, C., Rutter, M., Goode, S., Heemsbergen, J., Jordan, H., Mawhood, L., & Schopler, E. (1989). Autism diagnostic observation schedule: A standardized observation of communicative and social behavior. *J Autism Dev Disord, 19*(2), 185-212.

Lord, C., Rutter, M., & Le Couteur, A. (1994). Autism Diagnostic Interview-Revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J Autism Dev Disord, 24*(5), 659-685.

Magnée, M. J., De Gelder, B., Van Engeland, H., & Kemner, C. (2008). Audiovisual speech integration in pervasive developmental disorders: Evidence from event-related potentials. *Journal of Child Psychology and Psychiatry, 49*(9), 995-1000.

Magnée, M. J., Oranje, B., Van Engeland, H., Kahn, R. S., & Kemner, C. (2009). Cross-sensory gating in schizophrenia and autism spectrum disorder: EEG evidence for impaired brain connectivity? *Neuropsychologia, 47*(7), 1728-1732. doi: 10.1016/j.neuropsychologia.2009.02.012

Mahoney, J. R., Verghese, J., Dumas, K., Wang, C. L., & Holtzer, R. (2012). The effect of multisensory cues on attention in aging. *Brain Research, 1472*, 63-73.

Marco, E. J., Hinkley, L. B., Hill, S. S., & Nagarajan, S. S. (2011). Sensory processing in autism: A review of neurophysiologic findings. *Pediatr Res, 69*(5 Pt 2), 48R-54R. doi: 10.1203/PDR.0b013e3182130c54

Massaro, D. W., Cohen, M. M., & Smeele, P. M. (1996). Perception of asynchronous and conflicting visual and auditory speech. *J Acoust Soc Am, 100*(3), 1777-1786.

May, J. G., Williams, M. C., & Dunlap, W. P. (1988). Temporal order judgements in good and poor readers. *Neuropsychologia, 26*(6), 917-924.

McGrath, J., Saha, S., Chant, D., & Welham, J. (2008). Schizophrenia: A concise overview of incidence, prevalence, and mortality. *Epidemiol Rev, 30*, 67-76. doi: 10.1093/epirev/mxn001

McGurk, H., & MacDonald, J. (1976). Hearing lips and seeing voices. *Nature, 264*, 746-748.

Mittal, V. A., Ellman, L. M., & Cannon, T. D. (2008). Gene-environment interaction and covariation in schizophrenia: The role of obstetric complications. *Schizophr Bull, 34*(6), 1083-1094.

Mongillo, E. A., Irwin, J. R., Whalen, D. H., Klaiman, C., Carter, A. S., & Schultz, R. T. (2008). Audiovisual processing in children with and without Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders, 38*, 1349-1358.

Morein-Zamir, S., Soto-Faraco, S., & Kingstone, A. (2003). Auditory capture of vision: Examining temporal ventriloquism. *Brain research. Cognitive brain research, 17*(1), 154-163.

Mottron, L., & Burack, J. (2001). Enhanced perceptual functioning in the development of autism. In C. Y. Burack & Zelazo (Eds.), *The development of autism: Perspectives from theory and research* (pp. 131-148). Mahwah, NJ: Erlbaum.

Munhall, K. G., Gribble, P., Sacco, L., & Ward, M. (1996). Temporal constraints on the McGurk effect. *Percept Psychophys, 58*(3), 351-362.

Nagarajan, S., Mahncke, H., Salz, T., Tallal, P., Roberts, T., & Merzenich, M. M. (1999). Cortical auditory signal processing in poor readers. *Proceedings of the National Academy of Sciences of the United States of America, 96*(11), 6483-6488. doi: 10.1073/pnas.96.11.6483

Nusbaum, N. J. (1999). Aging and sensory senescence. *Southern Medical Journal, 92*(3), 267-275.

O'Neill, M., & Jones, R. S. (1997). Sensory-perceptual abnormalities in autism: A case for more research? *J Autism Dev Disord, 27*(3), 283-293.

Parsons, B. D., Gandhi, S., Aurbach, E. L., Williams, N., Williams, M., Wassef, A., & Eagleman, D. M. (2013). Lengthened temporal integration in schizophrenia. *Neuropsychologia, 51*(2), 372-376. doi: 10.1016/j.neuropsychologia.2012.11.008

Pearl, D., Yodashkin-Porat, D., Katz, N., Valevski, A., Aizenberg, D., Sigler, M., . . . Kikinzon, L. (2009). Differences in audiovisual integration, as measured by McGurk phenomenon, among adult and adolescent patients with schizophrenia and age-matched healthy control groups. *Comprehensive Psychiatry, 50*(2), 186-192. doi: 10.1016/j.comppsych.2008.06.004

Peiffer, A. M., Mozolic, J. L., Hugenschmidt, C. E., & Laurienti, P. J. (2007). Age-related multisensory enhancement in a simple audiovisual detection task. *Neuroreport, 18*(10), 1077-1081.

Peled, A., Ritsner, M., Hirschmann, S., Geva, A. B., & Modai, I. (2000). Touch feel illusion in schizophrenic patients. *Biological Psychiatry, 48*(11), 1105-1108. doi: 10.1016/s0006-3223(00)00947-1

Phillips, W. A., & Silverstein, S. M. (2003). Convergence of biological and psychological perspectives on cognitive coordination in schizophrenia. *Behavioral and Brain Sciences, 26*(1), 65-+. doi: 10.1017/s0140525x03000025

Poliakoff, E., Shore, D. I., Lowe, C., & Spence, C. (2006). Visuotactile temporal order judgments in ageing. *Neuroscience Letters, 396*(3), 207-211. doi: 10.1016/j.neulet.2005.11.034

Powers, A. R., Hillock, A. R., & Wallace, M. T. (2009). Perceptual training narrows the temporal window of multisensory binding. *J Neurosci, 29*(39), 12265-12274. doi: 10.1523/JNEUROSCI.3501-09.2009

Pöppel, E., Schill, K., & Von Steinbüchel, N. (1990). Sensory integration within temporally neutral systems states: A hypothesis. *Naturwissenschaften, 77*(2), 89-91.

Radeau, M. (1994). Auditory-visual spatial interaction and modularity. *Cahiers de Psychologie Cognitive-Current Psychology of Cognition, 13*(1), 3-51.

Ramus, F. (2003). Developmental dyslexia: specific phonological deficit or general sensorimotor dysfunction? *Current Opinion in Neurobiology, 13*(2), 212-218. doi: 10.1016/s0959-4388(03)00035-7

Rhodes, M. G. (2004). Age-related differences in performance on the Wisconsin card sorting test: A meta-analytic review. *Psychol Aging, 19*(3), 482-494.

Ross, L. A., Saint-Amour, D., Leavitt, V. M., Molholm, S., Javitt, D. C., & Foxe, J. J. (2007). Impaired multisensory processing in schizophrenia: Deficits in the visual enhancement of speech comprehension under noisy environmental conditions. *Schizophrenia Research, 97*(1-3), 173-183. doi: 10.1016/j.schres.2007.08.008

Russo, N., Foxe, J. J., Brandwein, A. B., Altschuler, T., Gomes, H., & Molholm, S. (2010). Multisensory processing in children with autism: High-density electrical mapping of auditory somatosensory integration. *Autism Research, 3*(5), 253-267. doi: 10.1002/aur.152

Scheier, C. R., Nijhawan, R., & Shimojo, S. (1999). Sound alters visual temporal resolution. *Investigative Ophthalmology & Visual Science, 40*, 4169.

Setti, A., Finnigan, S., Sobolewski, R., McLaren, L., Robertson, I. H., Reilly, R. B., . . . Newell, F. N. (2011). Audiovisual temporal discrimination is less efficient with aging: An event-related potential study. *Neuroreport, 22*(11), 554-558. doi: 10.1097/WNR.0b013e328348c731

Shams, L., Kamitani, Y., & Shimojo, S. (2002). Visual illusion induced by sound. *Brain Res Cogn Brain Res, 14*(1), 147-152.

Skottun, B. C., & Skoyles, J. R. (2006). Attention, dyslexia, and the line-motion illusion. *Optometry and Vision Science, 83*(11), 843-849.

Slutsky, D. A., & Recanzone, G. H. (2001). Temporal and spatial dependency of the ventriloquism effect. *Neuroreport, 12*(1), 7-10. doi: 10.1097/00001756-200101220-00009

Smith, E. G., & Bennetto, L. (2007). Audiovisual speech integration and lipreading in autism. *Journal of Child Psychology and Psychiatry, 48*(8), 813-821.

Stein, B., & Meredith, M. A. (1993). *The merging of the senses*. Cambridge MA: The MIT Press.

Stein, J. (2003). Visual motion sensitivity and reading. *Neuropsychologia, 41*(13), 1785-1793. doi: 10.1016/s0028-3932(03)00179-9

Stekelenburg, J. J., Maes, J. P., van Gool, A. R., Sitskoorn, M., & Vroomen, J. (In press). Deficient multisensory integration in schizophrenia: An event-related potential study. *Schizophrenia Research*. doi: 10.1016/j.schres.2013.04.038

Stekelenburg, J. J., & Vroomen, J. (2005). An event-related potential investigation of the time-course of temporal ventriloquism. *Neuroreport, 16*, 641-644.

Stephen, J. M., Knoefel, J. E., Adair, J., Hart, B., & Aine, C. J. (2010). Aging-related changes in auditory and visual integration measured with MEG. *Neuroscience Letters, 484*(1), 76-80. doi: 10.1016/j.neulet.2010.08.023

Stone, D. B., Urrea, L. J., Aine, C. J., Bustillo, J. R., Clark, V. P., & Stephen, J. M. (2011). Unisensory processing and multisensory integration in schizophrenia: A high-density electrical mapping study. *Neuropsychologia, 49*(12), 3178-3187. doi: 10.1016/j.neuropsychologia.2011.07.017

Szelag, E., Kowalska, J., Galkowski, T., & Pöppel, E. (2004). Temporal processing deficits in high-functioning children with autism. *British Journal of Psychology, 95*, 269-282.

Szycik, G. R., Munte, T. F., Dillo, W., Mohammadi, B., Samii, A., Emrich, H. M., & Dietrich, D. E. (2009). Audiovisual integration of speech is disturbed in schizophrenia: An fMRI study. *Schizophrenia Research, 110*(1-3), 111-118. doi: 10.1016/j.schres.2009.03.003

Talay-Ongan, A., & Wood, K. (2000). Unusual sensory sensitivities in autism: A possible crossroads. *International Journal of Disability, Development and Education, 47*, 201-212.

Tallal, P. (1980). Auditory temporal perception, phonics and reading disabilities in children. *Brain and Language, 9*(2), 182-198.

Tallal, P., Miller, S., & Fitch, R. H. (1993). Neurobiological basis of speech: A case for the pre-eminence of temporal processing. *Ann N Y Acad Sci, 682*, 27-47.

Taylor, N., Isaac, C., & Milne, E. (2010). A comparison of the development of audiovisual integration in children with Autism Spectrum Disorders and typically developing children. *Journal of Autism and Developmental Disorders, 40*(11), 1403-1411. doi: 10.1007/s10803-010-1000-4

Tommerdahl, M., Tannan, V., Holden, J. K., & Baranek, G. T. (2008). Absence of stimulus-driven synchronization effects on sensory perception in autism: Evidence for local underconnectivity? *Behavioral and Brain Functions, 4*. doi: 10.1186/1744-9081-4-19

Van den Stock, J., De Jong, S. J., Hodiamont, P. P. G., & De Gelder, B. (2011). Perceiving emotions from bodily expressions and multisensory integration of emotion cues in schizophrenia. *Social Neuroscience, 6*(5-6), 537-547. doi: 10.1080/ 17470919.2011.568790

Van der Burg, E., Olivers, C. N. L., Bronkhorst, A. W., & Theeuwes, J. (2008). Pip and pop: Nonspatial auditory signals improve spatial visual search. *Journal of Experimental Psychology-Human Perception and Performance, 34*(5), 1053-1065. doi: 10.1037/0096-1523.34.5.1053

Van der Smagt, M. J., Van Engeland, H., & Kemner, C. (2007). Brief report: Can you see what is not there? Low-level auditory-visual integration in Autism Spectrum Disorder. *Journal of Autism and developmental disorders, 37*, 2014-2019.

Van Wassenhove, V., Grant, K. W., & Poeppel, D. (2007). Temporal window of integration in auditory-visual speech perception. *Neuropsychologia, 45*(3), 598-607. doi: 10.1016/j.neuropsychologia.2006.01.001

Vatakis, A. (2013). The role of stimulus properties and cognitive processes in the quality of the multisensory perception of synchrony. In L. Albertazzi (Ed.), *The handbook of experimental phenomenology: Visual perception of shape, space and appearance* (pp. 243-263). Malden, MA, USA: Wiley-Blackwell.

Vellutino, F. R., Fletcher, J. M., Snowling, M. J., & Scanlon, D. M. (2004). Specific reading disability (dyslexia): What have we learned in the past four decades? *Journal of Child Psychology and Psychiatry, 45*(1), 2-40. doi: 10.1046/j.0021-9630.2003.00305.x

Virsu, V., Lahti-Nuuttila, P., & Laasonen, M. (2003). Crossmodal temporal processing acuity impairment aggravates with age in developmental dyslexia. *Neuroscience Letters, 336*(3), 151-154. doi: 10.1016/s0304-3940(02)01253-3

Vroomen, J., & De Gelder, B. (2004). Temporal ventriloquism: Sound modulates the flash-lag effect. *Journal of Experimental Psychology: Human Perception and Performance, 30*(3), 513-518.

Vroomen, J., & Keetels, M. (2006). The spatial constraint in intersensory pairing: No role in temporal ventriloquism. *Journal of Experimental Psychology: Human Perception and Performance, 32*(4), 1063-1071.

Vroomen, J., & Keetels, M. (2010). Perception of intersensory synchrony: A tutorial review. *Attention Perception & Psychophysics, 72*(4), 871-884. doi: 10.3758/app.72.4.871

Wallace, M. (2004). The development of multisensory integration. In G. A. Calvert, C. Spence & B. E. Stein (Eds.), *The handbook of multisensory processes* (pp. 625-642). Cambridge MA: MIT.

Waterhouse, S. (1999). *A positive approach to autism*. London: Jessica Kingsley Publishers.

Weiss, A. D. (1963). Auditory perception in relation to age. In J. E. Birren, R. N. Butler, S. W. Greenhouse, L. Sokoloff & M. R. Yarrow (Eds.), *Human aging: A biological and behavioral study* (pp. 111-140). Bethesda, MD, US: United States Department of Health, Education and Wealthfare.

Welch, R. B., & Warren, D. H. (1980). Immediate perceptual response to intersensory discrepancy. *Psychological Bulletin, 88*(3), 638-667.

Williams, L. E., Light, G. A., Braff, D. L., & Ramachandran, V. S. (2010). Reduced multisensory integration in patients with schizophrenia on a target detection task. *Neuropsychologia, 48*(10), 3128-3136. doi: 10.1016/j.neuropsychologia.2010.06.028

Zampini, M., Guest, S., & Shore, D. I. (2005). Audio-visual simultaneity judgments. *Perception & Psychophysics, 67*(3), 531-544. doi: 10.3758/bf03193329

Zampini, M., Shore, D. I., & Spence, C. (2003). Audiovisual temporal order judgments. *Experimental Brain Research, 152*(2), 198-210. doi: 10.1007/s00221-003-1536-z

Ziegler, J. C., & Goswami, U. (2005). Reading acquisition, developmental dyslexia, and skilled reading across languages: A psycholinguistic grain size theory. *Psychological Bulletin, 131*(1), 3-29. doi: 10.1037/0033-2909.131.1.3

Chapter 2

Sound improves diminished visual temporal sensitivity in schizophrenia

De Boer-Schellekens, L.
Stekelenburg, J.J.
Maes, J.P.
Van Gool, A.R.
Vroomen, J.

Acta Psychologica, in press

Abstract

Visual temporal processing and Multisensory Integration (MSI) of sound and vision was examined in individuals with schizophrenia using a visual Temporal Order Judgment (TOJ) task. Compared to a non-psychiatric control group, persons with schizophrenia were less sensitive judging the temporal order of two successively presented visual stimuli. However, their sensitivity to visual temporal order improved as in the control group when two accessory sounds were added (temporal ventriloquism). These findings indicate that individuals with schizophrenia have diminished sensitivity to visual temporal order, but no deficits in the integration of low-level auditory and visual information.

Introduction

The brain continuously gathers information via our different sensory channels. In order to make sense of these sensory inputs, our brain has to properly integrate these information sources into one coherent multisensory percept. Conceivably, a deficit in Multisensory Integration (MSI) can lead to difficulties in attributing a meaning to incoming stimuli and consequently misinterpretation and miscommunication. Schizophrenia is characterized by cognitive deficits and processing abnormalities at the behavioral and neural level in a number of sensory modalities (Williams, Light, Braff, & Ramachandran, 2010). Given that sensory systems need to cooperate and that their information needs to be combined, it is hypothesized that MSI might be impaired in schizophrenia as well.

Numerous studies have reported unisensory deficits in schizophrenia (Foxe, Doniger, & Javitt, 2001; Giersch et al., 2009; Lalor, De Sanctis, Krakowski, & Foxe, 2012; Rosburg, Boutros, & Ford, 2008; e.g., Silverstein & Keane, 2011 for a review on vision in schizophrenia; Stone et al., 2011), but only a few have focused on MSI. Most of these studies examined the integration of audiovisual information of speech (De Gelder, Vroomen, Annen, Masthof, & Hodiamont, 2002; Pearl et al., 2009; Ross et al., 2007; Szycik et al., 2009), and the audiovisual processing of emotional stimuli (for example De Gelder et al., 2005; De Jong, Hodiamont, Van den Stock, & De Gelder, 2009; Van den Stock, De Jong, Hodiamont, & De Gelder, 2011). The overall consensus is that higher-order audiovisual integration is likely impaired in individuals with schizophrenia. For example, a study by De Gelder et al. (2002) examined audiovisual interactions in sound localization (spatial ventriloquism) and speech, using a variant of the 'McGurk phenomenon' (McGurk & MacDonald, 1976). The results showed a normal pattern of performance of the individuals with schizophrenia in the spatial localization task, but patients showed impairments in the audiovisual (AV) integration of speech. This made the authors suggest that the MSI problem of schizophrenia individuals is not general, but confined to speech processing. Later studies by Pearl et al. (2009) and Ross et al. (2007) also found audiovisual integration deficits in speech in individuals with schizophrenia, although an fMRI-study on the 'McGurk effect' by Surguladze et al. (2001) found that schizophrenia individuals were as susceptible as the control group to the 'McGurk effect'. A recent study by Martin et al. (2013) also found no significant differences in the 'McGurk effect' between patients with schizophrenia and matched controls and no major differences in recognition of auditory or visual speech alone suggesting that patients with schizophrenia do not always show major deficits in AV speech integration.

A majority of the MSI studies in schizophrenia have focused on higher-order social processing, but it has not been fully examined whether integration deficits are also manifest at more basic levels with non-social stimuli. In a study by Magnée et al. (2009), individuals with schizophrenia were compared to individuals with Autism Spectrum Disorder (ASD) and a non-psychiatric control group on low-level audiovisual interactions using cortical EEG activation. They used a cross-sensory P50 suppression paradigm and found that atypical cross-sensory suppression was present in individuals with schizophrenia, but absent in individuals with ASD. According to the authors, these results imply that individuals with schizophrenia indeed also have difficulties with the processing of low-level audiovisual information (Magnée et al., 2009). A study by Williams et al. (2010) used reaction times (RTs) on a target detection task with simple visual, auditory and temporally congruent audiovisual stimuli to examine MSI in schizophrenia. The audiovisual targets were expected to be detected faster than unimodal targets, an effect known as 'intersensory facilitation'. The schizophrenia group was less facilitated detecting bimodal targets relative to non-psychiatric individuals, also indicating that schizophrenia patients are impaired in MSI of low-level interactions. However, other studies on low-level audiovisual integration found opposite results. De Gelder et al. (2002) reported no integration problems for the schizophrenia individuals in sound localization with audiovisual stimuli evoking a ventriloquist illusion. Another example of MSI is the 'rubber hand illusion' where the position of the felt hand is displaced in the direction of a visual fake hand. Peled et al. (2000) reported that individuals with schizophrenia showed a stronger (not weaker) 'rubber hand illusion' that also occurred more rapidly in patients than in controls. Foucher et al. (2007) elaborated on this idea and argued that individuals with schizophrenia sometimes display more MSI than controls because the time at which they perceive two stimuli as simultaneous, their 'window of simultaneity', is lengthened. In their task, participants judged whether two stimuli (either two auditory, two visual, or one auditory the other visual) were experienced as simultaneous or sequential. Compared to controls, patients needed larger inter-stimulus intervals (ISI) in auditory, visual, and audiovisual stimuli to experience the two stimuli as sequential, which possibly reflects an abnormally low time resolution in patients with schizophrenia.

In the current study, we further examined the idea of lowered temporal resolution and its consequence for MSI in persons with schizophrenia using a phenomenon known as 'temporal ventriloquism'. The basic finding is that an abrupt click sound can attract the appearance of when a flash occurs in time. A sound before a flash (at 100 ms) can make a flash appear earlier, and a sound after the flash (also at 100 ms) can make the flash appear later (Morein-Zamir, Soto-Faraco, & Kingstone, 2003; Scheier, Nijhawan, & Shimojo, 1999; Stekelenburg & Vroomen, 2005; Vroomen & De Gelder, 2004; Vroomen & Keetels, 2006; for a review see Vroomen & Keetels, 2010). One way to demonstrate this is by means of a visual Temporal Order Judgment (TOJ) task where participants judge which of two flashes appeared first. When two click sounds are added, one before the first flash and one after the second flash, sensitivity to visual temporal order improve because the apparent perceived Stimulus Onset Asynchrony (SOA) between the two flashes is increased.

This task allowed us to address two questions, namely whether individuals with schizophrenia have (1) diminished sensitivity to visual temporal order and (2) whether clicks improve their sensitivity to visual temporal order due to MSI in the form of temporal ventriloquism. If people with schizophrenia suffer from impairments in MSI *per se*, they should have a *diminished* temporal ventriloquist effect because click sounds are not well-integrated with flashes. Alternatively, if their temporal resolution is abnormal, then sensitivity to visual temporal order will be impaired. To the best of our knowledge, this is the first study examining possible impairments in low-level audiovisual integration in patients with schizophrenia based on a unimodal TOJ task.

Methods

Participants

Originally, 36 participants were included in and completed this study, but four participants were excluded from analysis (for more details, see results section). Therefore, 16 adults with schizophrenia and 16 non-psychiatric controls are described here (see Table 1 for a demographic and clinical overview). Both groups were matched on age ($t(30)$=-.668, p=.51) and gender and groups did not significantly differ on educational level (Mann-Whitney U=155.0, p=.84). The patient group was recruited from *Yulius Mental Health Institution*, Dordrecht, The Netherlands. The schizophrenia participants were all stable and chronic outpatients under ambulatory care. They were all on antipsychotic medication and seven patients were on co-medication (lorazepam, oxazepam, propranolol, citalopram, clomipramine, biperiden). Inclusion criteria for both psychiatric and non-psychiatric participants were: 18-55 years of age, no history of electroconvulsive treatment, no history of neurological illness, no history of alcohol or drug dependence or abuse within the last year, or long duration (>1 year) of past abuse, no medications which would grossly affect the EEG (e.g., barbiturates, as an EEG experiment was also part of the experimental procedures, see Stekelenburg et al., in press), normal hearing and normal or corrected-to-normal vision, an ability and desire to cooperate with our experimental procedures as evinced by giving informed consent. All patients met DSM-IV-TR criteria for schizophrenia based both on chart information and on the relevant module of the Mini-International Neuropsychiatric Interview (M.I.N.I.), which is a short, structured diagnostic interview for DSM-IV-TR and ICD-10 disorders that is designed to perform a short but accurate structured psychiatric interview (Sheehan et al., 1998). Severity of the symptoms was obtained using the Brief Psychiatric Rating Scale (BPRS). The non-psychiatric control group was recruited through a newspaper advertisement. All participants were tested individually and were unaware of the purpose of the experiment. Participants received 35 Euro for their participation. The study procedures were approved by the Medical Review Ethics Committee of the St. Elisabeth Hospital, Tilburg, The Netherlands, and were conducted in accordance with the Declaration of Helsinki.

Table 1. Demographic and Clinical Characteristics of Schizophrenia Patients and Non-Psychiatric Controls, Just Noticeable Differences (JND) in ms and Standard Deviations per Condition

	Schizophrenic patients		Non-psychiatric controls
N	16		16
Gender	15 male		15 male
Age (years)	40 (8.1)		36.4 (8.1)
Educational level			
Primary	1		-
Secondary	11		11
Tertiary	4		5
Illness duration (years)	16.6 (5.3)		-
BPRS total score	42.3 (11.5)		-
Chlorpromazine equivalents	693.7 (97.3) (range: 300-1500)[1]		-
Antipsychotic medication	*N*	*Mean daily dosage in mg (range)*	
Clozapine	7	546.4 (125-1000)	
Olanzapine	6	20.4 (10-40)	
Risperidone	1	4	
Bromperidol	1	2	
Haloperidol	1	10	
Co-medication			
Lorazepam	2	1	
Oxazepam	2	27.5 (15-40)	
Citalopram	1	20	
Propranolol	1	30	
Clomipramine	1	300	
Biperiden	1	6	
JND per condition (ms)			
Visual-only	39.6 (26.1)		28.5 (3.29)
~0 ms	25.7 (10.4)		21.1 (4.9)
~100 ms	21.5 (5.1)		18.1 (3.4)
~200 ms	27.3 (9.9)		20.3 (6.9)
~300 ms	28.0 (20.6)		20 (3.4)

[1] Chlorpromazine equivalents were calculated as in Gardner et al. (2010), except for one equivalent, which was calculated using the Dutch SPC (*http://db.cbg-meb.nl/IB-teksten/h10194.pdf*, Medicines Evaluation Board) for bromperidol and Jansen et al. (2004) as bromperidol equivalent doses were not available in Gardner et al. (2010).

Stimuli

Stimuli and procedures were similar to previous studies (e.g., Vroomen & Keetels, 2006) and were optimized to examine a temporal ventriloquist effect over an extended range of sound-light intervals. The visual stimuli were presented on a 15-inch laptop monitor (Dell Latitude 5500), controlled by E-Prime (Psychology Software Tools, Inc.; *http://www.pstnet.com/eprime*). Two white squares (diameter of 1.5 cm) were presented against a dark background at variable SOAs in two gray placeholders (diameter of 3.5 cm). The squares were presented at 2.4 degrees above and below a central fixation cross (see Figure 1). The auditory stimuli consisted of two short white noise clicks of 2 ms at 71 dB(A) presented through a headphone. A small red cross served as a fixation point and was placed at eye-level, at central location, approximately 60 cm in front of the participant. There were two within-subject factors. The first is the audiovisual interval between the onsets of the first-sound-and-first-light and the second-light-and-second-sound (4 intervals: ~0 ms, ~100 ms, ~200 ms, or ~300 ms, plus a visual-only condition serving as baseline) that allowed us to measure the (possibly expanded) temporal window of integration in a systematic way. The second factor is the stimulus onset asynchrony (SOA) between the upper and lower square (10 levels: ±83 ms, ±67 ms, ±50 ms, ±33 ms and ±16 ms, with negative values indicating that the lower visual stimulus was presented first). This resulted in 50 unique trials, each presented eight times in total in four blocks of 100 trials each. Within blocks, all combinations of SOA and audiovisual intervals were varied randomly.

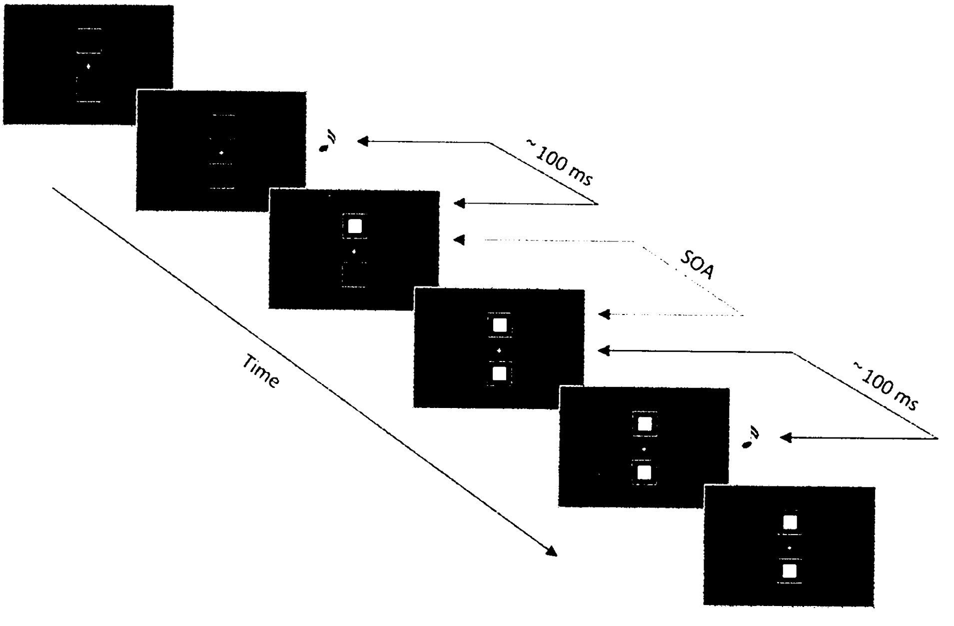


Figure 1: Set-up visual TOJ task with example of ~100 ms audiovisual interval

Procedure
Participants were tested individually in a dimly-lit room (either at Tilburg University or at *Yulius*). A red fixation light was illuminated at the beginning of the experiment and participants were instructed to maintain fixation during testing. Each trial consisted of the onset of the first visual stimulus and, after a variable SOA, the second visual stimulus was presented. The two squares remained on the screen until a response was made. Two sounds were presented, one before the first light and the other after the second light, at various audiovisual intervals. Participants were instructed not to pay attention to the sounds, as they did not predict in any sense which stimulus appeared first. Participants judged whether the upper or the lower square appeared first by pressing a corresponding key on a response box. The next trial started ~800 ms after a response was given. Responses were unspeeded with emphasis on accuracy. A practice session preceding the test was given in which trials were presented at the two longest SOAs for each condition. During practice, participants received feedback ('Wrong' or 'Correct') after each trial. Practice continued until six consecutive correct answers were given, where after testing started without feedback. There was a short pause after each block.

Results

Trials of the practice session were excluded from analyses. The individual proportion of 'upper light first' responses was calculated for each combination of stimulus condition and SOA, and then converted into equivalent Z-scores (analyzed as in previous studies by Keetels & Vroomen, 2005, and Vroomen & Keetels, 2006)[2]. For each condition, the best fitting straight line was calculated over the ten SOAs. The lines' slopes and intercepts were used to determine the just noticeable difference (JND=.675/slope) and the point of subjective simultaneity (PSS). The JND represents the smallest interval between two stimuli needed by participants to correctly judge which stimulus came first. A small JND thus represents good sensitivity, as smaller stimulus differences are required for correctly judging temporal order.

The group-averaged proportion of 'upper light first' responses are plotted in Figure 2, and the corresponding JNDs for each audiovisual interval are presented in Figure 3. As is clearly visible, the schizophrenia group had overall larger JNDs (they were less sensitive) than the non-psychiatric control group. For both groups alike, though, the largest JND was obtained in the visual-only condition, and the presence of the two sounds substantially

[2] For both groups JNDs were initially computed by fitting both logistic and linear functions. The results of the logistic and linear slopes and JNDs were equivalent. The linear function provided a significantly better fit to the data of the three conditions than the logistic function for both groups, and was therefore used as the principle function. However, the results of four subjects (two in both groups) could neither be fitted by a logistic or a linear function. They were therefore excluded from further analyses. The mean and standard deviations of R^2 for the non-psychiatric control group were .82(±.07), .82(±.07), .85(±.06), .75(±.13) and .83(±.06) for the five conditions (visual-only, ~0, ~100, ~200 and ~300 ms audiovisual delay) and .70(±.15), .82(±.09), .79(±.10), .77(±.11) and .76(±.17) for the schizophrenia group.

improved sensitivity in both groups. For both groups, sensitivity was numerically best at an audiovisual interval of ~100 ms. This was confirmed in a 2 (Groups; schizophrenia individuals versus non-psychiatric individuals) x 5 (Audiovisual Intervals; visual-only, ~0, ~100, ~200 and ~300 ms) overall repeated measures ANOVA on the JNDs. There was a main effect of Group $F(1,30)=4.67$, $p<.05$, $\eta p2=.14$, indicating that, on average, the schizophrenia group was less sensitive for visual temporal order than the non-psychiatric group (28.4 ms vs. 21.6 ms for the schizophrenia group and the non-psychiatric control group, respectively). There was also a main effect of Audiovisual Interval $F(4,28)=6.06$, $p<.01$, $\eta p2=.17$, mainly because sounds improved sensitivity. The Group x Audiovisual Interval interaction was not significant ($F<1$, $p=.75$), thus showing that sounds had essentially the same beneficial effect on both groups. Separate t-tests (Bonferroni corrected for multiple comparisons) confirmed that the JND in the ~100 ms audiovisual interval was the smallest and differed from the other audiovisual intervals (all p's<.05, except for the ~300 ms audiovisual interval which had a large variance). These results indicate that for both groups sensitivity improved when sounds were present rather than absent (a temporal ventriloquism effect).

For completeness, similar analyses were run on the PSS which represents the average interval by which one visual stimulus (the upper or lower) has to lead the other for being perceived as simultaneous. An overall 2 (Group) x 5 (Audiovisual Intervals) ANOVA on the PSS showed a main effect of Group $F(1,31)=5.13$, $p<.05$, indicating that the schizophrenia group showed overall more 'upper light first' responses (mean PSS=10.1 ms) than the non-psychiatric control group (mean PSS=-5.0 ms). There was also an Audiovisual Interval effect $F(4,28)=7.39$, $p<.01$, which showed that the groups had more 'lower light first' responses in the visual-only and ~0 ms audiovisual intervals (mean PSS of -6.3 ms and -1.5 ms, respectively) and more 'upper light first' responses for the ~100, ~200 and ~300 ms audiovisual intervals (mean PSS of 6.5 ms, 6.8 ms and 7.1 ms, respectively). Additional t-tests (Bonferroni corrected for multiple comparisons) confirmed that the differences in PSSs in the visual-only and ~0 ms audiovisual intervals were significant compared to the audiovisual intervals, all p's<.05 (except the ~0 ms audiovisual interval from the ~300 ms audiovisual interval), but not from each other, $p=1.0$. The audiovisual intervals ~100 ms, ~200 ms and ~300 ms did not differ compared to each other (all p's=1.0).

To assess whether sensitivity for visual temporal order in the schizophrenia group was associated with clinical scores or chlorpromazine equivalents, we computed the zero-order correlation (Pearson r) between the JNDs of the TOJ task with the BPRS total score, BPRS positive and negative symptoms scores and the chlorpromazine equivalents. We did not find any correlation to be significant (all p-values at least >.12). This indicates that diminished sensitivity to visual temporal order in people with schizophrenia is not (directly) correlated to the dosage of medication or to the severity of the symptoms as obtained by the BPRS.

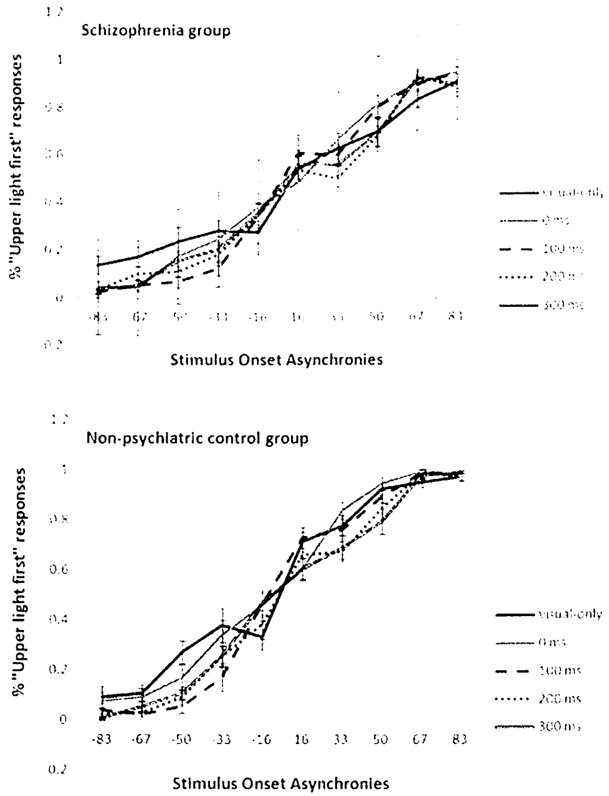


Figure 2. Group averaged proportion of 'upper light first' responses (error bars represent one standard error of the mean)

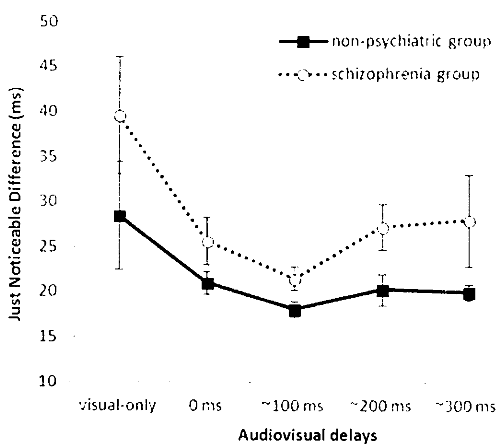


Figure 3. Group averaged JNDs as a function of the interval between the sound and the flash (error bars represent one standard error of the mean)

Discussion

This is the first study that examines audiovisual integration in individuals with schizophrenia using a (unimodal) visual TOJ task with click sounds that evoked temporal ventriloquism. We found that, compared to non-psychiatric controls, persons with schizophrenia were less sensitive judging visual temporal order, and they thus needed more time between two successively presented visual stimuli to correctly judge their order. Both groups, though, benefitted equally well from the presence of two click sounds that are known to improve sensitivity (temporal ventriloquism). This indicates that individuals with schizophrenia are less sensitive to visual temporal order than controls, but – at least in this paradigm – show no deficits in MSI of low-level audiovisual stimuli.

Our audiovisual integration results differ from findings of low-level audiovisual integration studies by Magnée et al. (2009) and Williams et al. (2010) who found MSI in schizophrenia individuals to be impaired. Although it is not quite clear what causes these opposite results, differences in experimental set-up, paradigm and stimuli may play an essential role here. Interestingly however, results from other studies are in line with our findings of intact MSI of low-level audiovisual stimuli. Studies by De Gelder et al. (2002), Peled et al. (2000) and Foucher et al. (2007) also found normal AV integration in persons with schizophrenia. Foucher et al. (2007) found that their patient group had greater simultaneity thresholds in visual, auditory and bimodal stimuli than the control group, so schizophrenia patients needed larger SOAs to perceive two stimuli as occurring 'one-after-the-other'. In a follow-up study, Giersch et al. (2009) found similar results of impairment in discriminating simultaneous from asynchronous stimuli by the schizophrenia patient group, which was not due to a bias effect or to attentional disturbances. Foucher et al. (2007) suggested that lengthened windows of simultaneity in individuals suffering from schizophrenia could account for the results of increased binding in MSI (see also Peled et al., 2000). Interestingly, though, in our study we did not find evidence in the patient group for increased binding of sounds and flashes at longer audiovisual intervals. Future studies might examine this by using a larger range of SOAs than here.

The notion of an increased window of simultaneity might, however, shed light on the reduced sensitivity for visual temporal order of the schizophrenia group. Foucher et al. (2007) argued that patients with schizophrenia do not judge the timing of events with the same resolution as healthy controls and linked this to abnormal functional integration in schizophrenia (Foucher et al., 2005), also known as 'dysconnectivity'. A large number of neurophysiological and neuroimaging studies with schizophrenia patients have found evidence for dysconnectivity (e.g., Cho, Konecky, & Carter, 2005; Friston, Frith, Fletcher, Liddle, & Frackowiak, 1996; Lawrie et al., 2002; Meyer-Lindenberg et al., 2005; Stephan, Baldeweg, & Friston, 2006; Symond, Harris, Gordon, & Williams, 2005; Uhlhaas et al., 2006) which can be seen as a core pathology of schizophrenia and an underlying mechanism for various symptoms of the disorder. Foucher et al. (2006) suggested that this abnormal functional integration may also possibly lengthen neural conduction times and, as a result, action potentials may be delayed and may not arrive in synchrony. This might provide an explanation for the diminished sensitivity for visual temporal order we found in our study. If individuals with schizophrenia do indeed need more time between two stimuli to judge them as 'one-after-the-other', they will be less sensitive to the temporal order of (in this case) the visual stimuli. Although, the question then remains why our results do not show any signs of an extended temporal window of integration as Foucher et al. (2007) did.

Several other studies on schizophrenia have examined the timing aspect, focusing on impairments in duration judgments, time perception, and temporal processing that characterize the schizophrenia disorder. Lalanne et al. (2012) compared a group of schizophrenia patients with non-psychiatric controls on a simultaneity judgment task and reported that patients have higher thresholds of asynchrony detection than controls. They found that patients detect asynchronies in a qualitative different way than the controls; in controls, elementary predictive mechanisms would allow anticipation of upcoming events, whereas patients appeared to process visual stimuli as if isolated rather than following each other. This made the authors suggest that patients with schizophrenia might suffer from a deficit in coding time-event structure. A study by Stekelenburg et al. (in press) (with the same patient and control group as in the current study) reported in an EEG study that in non-psychiatric controls visual information that predicts the onset of a sound (as in the video of a handclap) reduces the auditory-evoked N1 when compared to the N1 elicited in an auditory-only condition. This reduction of the N1 was absent in patients with schizophrenia, suggesting a deficit in audiovisual temporal prediction of sound. In a finger-tapping experiment with schizophrenia patients and non-psychiatric controls by Delevoye-Turrell et al. (2012), evidence for preserved internal clock in schizophrenia with normal spontaneous tapping tempo was reported, but with increased contact durations in the patient group. The authors suggest a specific problem in the fast integration of incoming haptic feedback with the outgoing motor efference copy. They proposed that schizophrenia patients have difficulties in distinguishing between the physical past and the present, so that the coding of the passage of time could be impaired with direct consequences on the capacity to correctly time and integrate sequences of multiple events. Other studies have shown a fundamental deficit in temporal auditory precision in schizophrenia (Carroll, O'Donnell, Shekhar, & Hetrick, 2009; Elvevåg et al., 2003; Lee et al., 2009). Taking these findings and our results together, this suggests the possibility that time perception abnormalities in schizophrenia could be part of neuropsychological dysfunction which might have influenced the schizophrenia group's performance on the visual TOJ.

Other speculations about reduced temporal visual sensitivity in schizophrenia can be derived from studies that have focused on visual integration deficits in contrast, contour, form, and motion processing (e.g., Butler, Silverstein, & Dakin, 2008; see Chen, 2011, for a review on visual motion; Stone et al., 2011). Problems with visual motion could, in particular, play a role because the spatio-temporal arrangement of visual stimuli in our and other visual TOJ tasks usually evokes apparent motion. If perception of apparent motion is indeed compromised in patients with schizophrenia, it likely interferes with judgments of visual temporal order.

Besides persons with schizophrenia being less sensitive judging visual temporal order, our PSS results also indicated that the schizophrenia group differed from the non-psychiatric group in their judgment of perceived simultaneity between the visual stimuli, as the schizophrenia group showed overall more 'upper light first' responses compared to the non-psychiatric group who showed more 'lower light first' responses. Although speculative, we want to discuss some possibilities. First, the PSS results could fit the 'dysconnectivity' hypothesis as mentioned before. If people with schizophrenia do not judge the timing of events with the same resolution as healthy controls as a result of abnormal functional integration, it seems likely that they need aberrant timing of events to be perceived as simultaneous. A study by Schmidt et al. (2011) found elevated simultaneity thresholds in patients with schizophrenia in an asynchrony detection task. The authors suggest that their findings show evidence for a generalized deficit in event-structure coding. In relation to this event-structure coding, Pöppel (1985) argued that at a fundamental level and in order to be able to structure which events come first, one needs to experience simultaneity as compared to asynchrony. If this capability is disturbed, the experience not only of simultaneity but of event-structure too, will become distorted. Disturbed event-structure coding might be a possible explanation for the relatively longer time the schizophrenia group needed to perceive simultaneity, but it does not explain why this group showed just more 'upper light first' responses.

One can also ask to which extent the beneficial effects of sounds on sensitivity to visual temporal order might be that an alerting effect triggered by the first sound. A study by Morein-Zamir et al. (2003) investigated this explanation using a visual TOJ task in which the first sound could appear at the same time as the first light or lead by 100 ms. Similarly, the second sound could appear at the same time as the second light, or trail by 100 ms. Their results ruled out an alerting explanation, as TOJ performance improvement was due to the presentation of the second sound after the second light and presenting a sound before the first light did not improve performance relative to the visual-only condition. In terms of temporal ventriloquism, the second sound thus biases the onset of the second light and intact audiovisual integration is required for this effect to occur.

It remains for future studies to examine whether our results can be generalized to different clinical sub-populations. The schizophrenia individuals in our study were all of normal intelligence. While the disorder is heterogeneous in origin, one should be cautious extrapolating the results to individuals suffering from intellectual disabilities or to individuals who are substantially older or younger than the group we studied. It also remains for future studies to examine whether the results can be generalized to non-medicated schizophrenia patients, as all of our individuals with schizophrenia were on antipsychotic medication. An effect of drug treatment cannot be ruled out, although no correlation was found between sensitivity for visual temporal order and treatment in chlorpromazine equivalents.

Summarized, our results showed that individuals with schizophrenia were less sensitive (e.g., they needed more time) to correctly judge the temporal order of successively presented visual stimuli. This is evidence for reduced visual temporal sensitivity compared to a non-psychiatric control group. However, the schizophrenia group showed equal amounts of temporal ventriloquism, indicating intact audiovisual integration of low-level stimuli.

References

Butler, P. D., Silverstein, S. M., & Dakin, S. C. (2008). Visual perception and its impairment in schizophrenia. *Biological Psychiatry, 64*(1), 40-47. doi: 10.1016/j.biopsych.2008-03.023

Carroll, C. A., O'Donnell, B. F., Shekhar, A., & Hetrick, W. P. (2009). Timing dysfunctions in schizophrenia span from millisecond to several-second durations. *Brain and Cognition, 70*, 181-190.

Chen, Y. (2011). Abnormal visual motion processing in schizophrenia: A review of research progress. *Schizophrenia Bulletin, 37*(4), 709-715. doi: 10.1093/schbul/sbr020

Cho, R. Y., Konecky, R. O., & Carter, C. S. (2005). Impairments in gamma band synchronization and context processing in schizophrenia. *Schizophrenia Bulletin, 31*(2), 450-451.

De Gelder, B., Vroomen, J., Annen, L., Masthof, E., & Hodiamont, P. P. G. (2002). Audio-visual integration in schizophrenia. *Schizophrenia Research, 59*, 211-218.

De Gelder, B., Vroomen, J., De Jong, S. J., Masthof, E. D., Trompenaars, F. J., & Hodiamont, P. P. G. (2005). Multisensory integration of emotional faces and voices in schizophrenics. *Schizophrenia Research, 72*, 195-203.

De Jong, J. J., Hodiamont, P. P. G., Van den Stock, J., & De Gelder, B. (2009). Audiovisual emotion recognition in schizophrenia: Reduced integration of facial and vocal affect. *Schizophrenia Research, 107*, 286-293.

Delevoye-Turrell, Y., Wilquin, H., & Giersch, A. (2012). A ticking clock for the production of sequential actions: Where does the problem lie in schizophrenia? *Schizophrenia Research, 135*(1-3), 51-54. doi: 10.1016/j.schres.2011.12.020

Elvevåg, B., McCormack, T., Gilbert, A., Brown, G. D. A., Weinberger, D. R., & Goldberg, T. E. (2003). Duration judgements in patients with schizphrenia. *Psychological Medicine, 33*, 1249-1261.

Foucher, J. R., Lacambre, M., Pham, B.-T., Giersch, A., & Elliott, M. A. (2007). Low time resolution in schizophrenia. Lengthened windows of simultaneity for visual, auditory and bimodal stimuli. *Schizophrenia Research, 97*, 118-127.

Foucher, J. R., Luck, D., Giersch, A., Lacambre, M., Pham, B. T., & Elliott, M. (2006). Lengthened windows of simultaneous perception in schizophrenia. *Schizophrenia Research, 81*, 121-121.

Foucher, J. R., Vidailhet, P., Chanraud, S., Gounot, D., Grucker, D., Pins, D., . . . Danion, J. M. (2005). Functional integration in schizophrenia: Too little or too much? Preliminary results on fMRI data. *Neuroimage, 26*(2), 374-388. doi: 10.1016/j.neuroimage.2005.01.042

Foxe, J. J., Doniger, G. M., & Javitt, D. C. (2001). Early visual, processing deficits in schizophrenia: impaired PI generation revealed by high-density electrical mapping. *Neuroreport, 12*(17), 3815-3820. doi: 10.1097/00001756-200112040-00043

Friston, K. J., Frith, C. D., Fletcher, P., Liddle, P. F., & Frackowiak, R. S. J. (1996). Functional topography: Multidimensional scaling and functional connectivity in the brain. *Cerebral Cortex, 6*(2), 156-164. doi: 10.1093/cercor/6.2.156

Gardner, D. M., Murphy, A. L., O'Donnell, H., Centorrino, F., & Baldessarini, R. J. (2010). International consensus study of antipsychotic dosing. *Am J Psychiatry, 167*(6), 686-693. doi: 10.1176/appi.ajp.2009.09060802

Giersch, A., Lalanne, L., Corves, C., Seubert, J., Shi, Z. H., Foucher, J., & Elliott, M. A. (2009). Extended visual simultaneity thresholds in patients with schizophrenia. *Schizophrenia Bulletin, 35*(4), 816-825. doi: 10.1093/schbul/sbn016

Janssen, B., Weinmann, S., Berger, M., & Gaebel, W. (2004). Validation of polypharmacy process measures in inpatient schizophrenia care. *Schizophr Bull, 30*(4), 1023-1033.

Keetels, M., & Vroomen, J. (2005). The role of spatial disparity and hemifields in audio-visual temporal order judgments. *Experimental Brain Research, 167*, 635-640.

Lalanne, L., van Assche, M., & Giersch, A. (2012). When predictive mechanisms go wrong: Disordered visual synchrony thresholds in schizophrenia. *Schizophrenia Bulletin, 38*(3), 506-513. doi: 10.1093/schbul/sbq107

Lalor, E. C., De Sanctis, P., Krakowski, M. I., & Foxe, J. J. (2012). Visual sensory processing deficits in schizophrenia: Is there anything to the magnocellular account? *Schizophrenia Research, 139*(1-3), 246-252. doi: 10.1016/j.schres.2012.05.022

Lawrie, S. M., Buechel, C., Whalley, H. C., Frith, C. D., Friston, K. J., & Johnstone, E. C. (2002). Reduced frontotemporal functional connectivity in schizophrenia associated with auditory hallucinations. *Biological Psychiatry, 51*(12), 1008-1011. doi: 10.1016/s0006-3223(02)01316-1

Lee, K.-H., Bhaker, R. S., Mysore, A., Parks, R. W., Birkett, P. B. L., & Woodruff, P. W. R. (2009). Time perception and its neuropsychological correlates in patients with schizophrenia and in healthy volunteers. *Psychiatry Research, 166*, 174-183.

Magnée, M. J., Oranje, B., Van Engeland, H., Kahn, R. S., & Kemner, C. (2009). Cross-sensory gating in schizophrenia and autism spectrum disorder: EEG evidence for impaired brain connectivity? *Neuropsychologia, 47*(7), 1728-1732. doi: 10.1016/j.neuropsychologia.2009.02.012

Martin, B., Giersch, A., Huron, C., & Van Wassenhove, V. (2013). Temporal event structure and timing in schizophrenia: Preserved binding in a longer 'now'. *Neuropsychologia, 51*(2), 358-371. doi: 10.1016/j.neuropsychologia.2012.07.002

McGurk, H., & MacDonald, J. (1976). Hearing lips and seeing voices. *Nature, 264*, 746-748.

Meyer-Lindenberg, A. S., Olsen, R. K., Kohn, P. D., Brown, T., Egan, M. F., Weinberger, D. R., & Berman, K. F. (2005). Regionally specific disturbance of dorsolateral prefrontal-hippocampal functional connectivity in schizophrenia. *Archives of General Psychiatry, 62*(4), 379-386. doi: 10.1001/archpsyc.62.4.379

Morein-Zamir, S., Soto-Faraco, S., & Kingstone, A. (2003). Auditory capture of vision: Examining temporal ventriloquism. *Brain research. Cognitive brain research, 17*(1), 154-163.

Pearl, D., Yodashkin-Porat, D., Katz, N., Valevski, A., Aizenberg, D., Sigler, M., . . . Kikinzon, L. (2009). Differences in audiovisual integration, as measured by McGurk phenomenon, among adult and adolescent patients with schizophrenia and age-matched healthy control groups. *Comprehensive Psychiatry, 50*(2), 186-192. doi: 10.1016/j.comppsych.2008.06.004

Peled, A., Ritsner, M., Hirschmann, S., Geva, A. B., & Modai, I. (2000). Touch feel illusion in schizophrenic patients. *Biological Psychiatry, 48*(11), 1105-1108. doi: 10.1016/s0006-3223(00)00947-1

Pöppel, E. (1985). Bridging a neuronal gap. Perceptual completion across a cortical scotoma is dependent on stimulus motion. *Naturwissenschaften, 72*(11), 599-600.

Rosburg, T., Boutros, N. N., & Ford, J. M. (2008). Reduced auditory evoked potential component N100 in schizophrenia - A critical review. *Psychiatry Research, 161*(3), 259-274. doi: 10.1016/j.psychres.2008.03.017

Ross, L. A., Saint-Amour, D., Leavitt, V. M., Molholm, S., Javitt, D. C., & Foxe, J. J. (2007). Impaired multisensory processing in schizophrenia: Deficits in the visual enhancement of speech comprehension under noisy environmental conditions. *Schizophrenia Research, 97*(1-3), 173-183. doi: 10.1016/j.schres.2007.08.008

Scheier, C. R., Nijhawan, R., & Shimojo, S. (1999). Sounds alters visual temporal resolution. *Investigative Ophthalmology & Visual Science, 40*, 4169.

Schmidt, H., McFarland, J., Ahmed, M., McDonald, C., & Elliott, M. A. (2011). Low-level temporal coding impairments in psychosis: Preliminary findings and recommendations for further studies. *Journal of Abnormal Psychology, 120*(2), 476-482. doi: 10.1037/a0023387

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., . . . Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (MINI): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry, 59*, 22-33.

Silverstein, S. M., & Keane, B. P. (2011). Perceptual organization impairment in schizophrenia and associated brain mechanisms: Review of research from 2005 to 2010. *Schizophrenia Bulletin, 37*(4), 690-699. doi: 10.1093/schbul/sbr052

Stekelenburg, J. J., Maes, J. P., Van Gool, A. R., Sitskoorn, M., & Vroomen, J. (in press). Deficient multisensory integration in schizophrenia: An event-related potential study. *Schizophrenia Research*. doi: 10.1016/j.schres.2013.04.038

Stekelenburg, J. J., & Vroomen, J. (2005). An event-related potential investigation of the time-course of temporal ventriloquism. *Neuroreport, 16*, 641-644.

Stephan, K. E., Baldeweg, T., & Friston, K. J. (2006). Synaptic plasticity and dysconnection in schizophrenia. *Biological Psychiatry, 59*(10), 929-939. doi: 10.1016/j.biopsych.2005.10.005

Stone, D. B., Urrea, L. J., Aine, C. J., Bustillo, J. R., Clark, V. P., & Stephen, J. M. (2011). Unisensory processing and multisensory integration in schizophrenia: A high-density electrical mapping study. *Neuropsychologia, 49*(12), 3178-3187. doi: 10.1016/j.neuropsychologia.2011.07.017

Surguladze, S. A., Calvert, G. A., Brammer, M. J., Campbell, R., Bullmore, E. T., Giampietro, V., & David, A. S. (2001). Audio-visual speech perception in schizophrenia: An fMRI study. *Psychiatry Research-Neuroimaging, 106*(1), 1-14. doi: 10.1016/s0925-4927(00)00081-0

Symond, M. B., Harris, A. W. F., Gordon, E., & Williams, L. M. (2005). 'Gamma synchrony' in first-episode schizophrenia: A disorder of temporal connectivity? *American Journal of Psychiatry, 162*(3), 459-465. doi: 10.1176/appi.ajp.162.3.459

Szycik, G. R., Munte, T. F., Dillo, W., Mohammadi, B., Samii, A., Emrich, H. M., & Dietrich, D. E. (2009). Audiovisual integration of speech is disturbed in schizophrenia: An fMRI study. *Schizophrenia Research, 110*(1-3), 111-118. doi: 10.1016/j.schres.2009.03.003

Uhlhaas, P. J., Linden, D. E. J., Singer, W., Haenschel, C., Lindner, M., Maurer, K., & Rodriguez, E. (2006). Dysfunctional long-range coordination of neural activity during Gestalt perception in schizophrenia. *Journal of Neuroscience, 26*(31), 8168-8175. doi: 10.1523/jneurosci.2002-06.2006

Van den Stock, J., De Jong, S. J., Hodiamont, P. P. G., & De Gelder, B. (2011). Perceiving emotions from bodily expressions and multisensory integration of emotion cues in schizophrenia. *Social Neuroscience, 6*(5-6), 537-547. doi: 10.1080/17470919.2011.568790

Vroomen, J., & De Gelder, B. (2004). Temporal ventriloquism: Sound modulates the flash-lag effect. *Journal of Experimental Psychology: Human Perception and Performance, 30*(3), 513-518.

Vroomen, J., & Keetels, M. (2006). The spatial constraint in intersensory pairing: No role in temporal ventriloquism. *Journal of Experimental Psychology: Human Perception and Performance, 32*(4), 1063-1071.

Vroomen, J., & Keetels, M. (2010). Perception of intersensory synchrony: A tutorial review. *Attention Perception & Psychophysics, 72*(4), 871-884. doi: 10.3758/app.72.4.871

Williams, L. E., Light, G. A., Braff, D. L., & Ramachandran, V. S. (2010). Reduced multisensory integration in patients with schizophrenia on a target detection task. *Neuropsychologia, 48*(10), 3128-3136. doi: 10.1016/j.neuropsychologia.2010.06.028

Chapter 3

Diminished sensitivity of audiovisual temporal order in autism spectrum disorder

De Boer-Schellekens, L.

Eussen, M.

Vroomen, J.

Frontiers in Integrative Neuroscience 2013; vol 7, article 8

Abstract

We examined sensitivity of audiovisual temporal order in adolescents with Autism Spectrum Disorder (ASD) using an audiovisual Temporal Order Judgment (TOJ) task. In order to assess domain-specific impairments, the stimuli varied in social complexity from simple flash/beeps to videos of a handclap or a speaking face. Compared to typically-developing controls, individuals with ASD were generally less sensitive in judgments of audiovisual temporal order (larger Just Noticeable Differences, JNDs), but there was no specific impairment with social stimuli. This suggests that people with ASD suffer from a more general impairment in audiovisual temporal processing.

Introduction

In the multisensory world we live in, we are constantly bombarded with information that reaches us through our different senses. The brain has to synthesize this mix of sensory information into one coherent multisensory percept. An example of this intersensory process is a speaker that can be seen and heard at the same time. This results in an ensemble of multiple features across the different senses that our brain has access to (i.e., lip movement, facial expression, speed and temporal structure of the speech sound) that ultimately leads to an increase in perceptual reliability. This sensory synthesis is a constantly occurring phenomenon that shapes our view of the world and it is therefore crucial for our everyday, social and adaptive behavior (Wallace, 2004). It also raises the question how our brain integrates this wealth of sensory information and how a coherent representation of the world is obtained (Keetels & Vroomen, 2012). Another question is what happens if the brain is impaired in integrating this mix of sensory input.

This is one of the issues raised in contemporary research in Autism Spectrum Disorder (ASD). In addition to traditional impairments in communication, social behavior and stereotyped repetitive movements, abnormalities in sensory processing are often reported in ASD. Indeed, several contemporary theories on ASD reflect the idea that sensory deficits are core symptoms of autism as well (Crane, Goddard, & Pring, 2009; Kern et al., 2007). In this view, sensory deficits might have downstream effects on the development of the perceptual system that may eventually lead to adverse consequences for communication and social interaction (Bertone, Mottron, Jelenic, & Faubert, 2005; Mottron & Burack, 2001).

Early clinical observations dating back to Kanner (1943) already emphasized sensory avoidance and a tendency to over-focus on local attributes. More recent accounts have proposed that autism is characterized by weak 'central coherence' (Frith, 1989). Central coherence is the everyday tendency to process incoming information in its context, pulling information together for higher-level meaning, often at the expense of memory for detail. Frith (1989) proposed that people with autism show detail-focused local processing in which features are perceived and retained at the expense of global configuration and contextualized meaning. Some have linked this to functional and/or neuroanatomical under-connectivity between brain areas (Brock, Brown, Boucher, & Rippon, 2002; Courchesne & Pierce, 2005). The distribution of attention to global/local features may be different in autism, leading one to predict relatively good performance where attention to local information is advantageous, but poor performance on tasks requiring the recognition of global meaning or integration of stimuli in context (Happé, 1999). Iarocci and McDonald (2006) suggest that many of the leading theories of autism allude to dynamic constructs and conceptualizations such as central coherence, temporal binding, shifting attention, enhanced perception and neural modulation and connectivity that may all eventually involve multisensory processing and integration.

Empirical evidence of multisensory processing deficits in ASD is growing and there are now several clinical and anecdotal reports that the sensory abnormalities that are observed among individuals with ASD involve more than one sensory modality (e.g., Brock et al., 2002; Frith, 1989; Happé, 2005; O'Neill & Jones, 1997). One piece of evidence in support of this notion comes from studies on the Multisensory Integration (MSI) of speech and emotions as perceived from the face and the voice. Several studies reported that persons with ASD may have less MSI (Bebko, Weiss, Demark, & Gomez, 2006; De Gelder, Vroomen, & Van der Heide, 1991; Magnée, De Gelder, Van Engeland, & Kemner, 2008; Mongillo et al., 2008; Russo et al., 2010; Smith & Bennetto, 2007). As an example, De Gelder et al. (1991) reported that individuals with ASD were normal in auditory speech perception and were unimpaired in silent lip-reading, but when the auditory and visual information streams were combined, there was very little effect of the lip-read information on auditory speech perception. Magnée et al. (2008) also observed that high-functioning adults with ASD had difficulties integrating heard and lip-read speech that could not be attributed to problems in abnormal low-level integration. Possibly, then, people with ASD may have a generalized deficit integrating information from different modalities (Brandwein et al., 2012; Foxe & Molholm, 2009; Kern et al., 2007; Mongillo et al., 2008; Oberman & Ramachandran, 2008).

Others, however, found MSI in people with ASD to be normal (Foss-Feig et al., 2010; Grossman, Schneps, & Tager-Flusberg, 2009; Van der Smagt, Van Engeland, & Kemner, 2007). Williams et al. (2004) reported that children with autism normally utilized visual information in identifying auditory speech. Children with autism could also determine – as typically developing (TD) controls did – whether the specific sound of a bouncing ball matched its physical appearance (Mongillo et al., 2008). Equivalent amounts of MSI between an ASD and TD group were also reported when participants were asked to detect the direction of two laterally separated beeps in the presence of concurrent visual apparent motion, or the number of flashes when concurrent beeps were present (Keane, Rosenthal, Chun, & Shams, 2010). When these results are taken together, there is thus no consensus as to what extent MSI is impaired in autism.

Research in ASD's (multi)sensory processing has mainly focused on the integration of higher-level information like speech or faces, but there has been far less interest in the underlying mechanism and the constraints under which information from different modalities is combined. In research on MSI, it is generally agreed that (near) temporal synchrony is *the* most important factor for MSI to occur (e.g., Radeau, 1994; Stein & Meredith, 1993; Welch & Warren, 1980). Intersensory integration thus will only occur if information from the different sensory modalities arrives at approximately the same time in the brain because otherwise two separate events are perceived. However, temporal synchrony between the senses is not straightforward, because there is no evidence of a dedicated sense organ that registers time in an absolute scale. It is well-known that the neural transduction times of the various sensory modalities differ significantly, and the brain thus has to overcome differences in transduction and neural transmission time (Pöppel, 1997; Vroomen & De Gelder, 2004). It is conceivable that if there are fundamental disturbances in the temporal orchestration of multisensory events, this will lead to deficits in multisensory processing as well. Brock et al. (2002) indeed theorized that the critical deficit of MSI in people with ASD may lie in the temporal synchronization among both local and distributed neural networks. These networks can show strong patterns of entrainment in response to a given sensory stimulus (i.e., a focus of activation in one area is soon followed in a strongly time-locked fashion by a focus in a second connected brain area), and this temporal synchronization among brain regions is likely to be critically important in the binding of multisensory stimuli into unified perceptual constructs (Senkowski, Schneider, Foxe, & Engel, 2008). A critical question is thus whether people with ASD do indeed suffer from intersensory temporal deficits that may underlie other impairments in MSI.

At present, autism studies on temporal processing are very limited, but some indeed report differences in various aspects of temporal functioning. Szelag et al. (2004) studied temporal processing in the time domain of a few seconds in children with ASD and found important deficits in duration judgments compared to TD children. In a study by Bebko et al. (2006), intermodal perception of audiovisual temporal synchrony in young children with autism was compared with children without impairments and a group of children with other developmental disabilities. The ASD group displayed reduced or no preference at all for synchronous over asynchronous audiovisual speech and non-speech stimuli, possibly because children with ASD are not (yet) sensitive to audiovisual temporal synchrony. Two recent studies, by Kwayke et al. (2011) and Foss-Feig et al. (2010), proposed that individuals with ASD may have an extended window of multisensory temporal binding. The study by Foss-Feig et al. (2010) used the sound-induced double-flash illusion in children with ASD. In this illusion, pairing of a single visual stimulus (i.e., flash) with several auditory stimuli (i.e., beeps) often results in the perception of two or more flashes (Shams, Kamitani, & Shimojo, 2000). Foss-Feig et al. (2010) reported that children with ASD had this flash-beep illusion over an extended range of Stimulus Onset Asynchronies (SOAs) relative to TD children. Kwayke et al. (2011) also reported an extended window of temporal integration in children with ASD using TOJ tasks with visual, auditory, and audiovisual stimuli. The authors reported no differences in sensitivity for visual temporal order, but thresholds were higher in ASD on the auditory TOJ task. In the multisensory TOJ task, the authors relied on the phenomenon known as 'temporal ventriloquism' (Scheier, Nijhawan, & Shimojo, 1999), where click sounds can improve sensitivity for visual temporal order if the clicks are presented within a certain time window. Children with ASD showed performance improvements over a wider range of temporal intervals than TD children, thus reinforcing the idea that children with ASD have a wider temporal window of MSI.

In this current study we presented adolescents with ASD and TD controls an audiovisual TOJ task to examine their sensitivity of intersensory temporal order in a direct way. Three kinds of stimuli were used that are known to differ on a number of potentially relevant dimensions: a flash/beep, a video of a handclap with the corresponding sound, and a video of a face articulating a syllable with the corresponding speech sound. The asynchrony between the audio and video was varied, and participants judged whether the auditory stimulus came 'early' or 'late' with respect to the video. By using different stimuli (flash/beep, handclap, speech), we varied the complexity of the stimuli that allowed us to examine whether people with ASD suffer from a general or a more specific impairment in audiovisual temporal processing. Previous studies with TD participants have shown that people are more sensitive to audiovisual timing differences of artificial stimuli than audiovisual speech (Dixon & Spitz, 1980) and that judging temporal order in audiovisual speech is particularly difficult, possibly because it lacks fast visual and auditory transients that can serve as temporal markers (Stekelenburg & Vroomen, 2007). The handclap condition was expected to be relatively easy for TD participants because it not only contains a fast audiovisual transient, but also visual information that predicts sound onset that may serve as a temporal anchor (Vroomen & Keetels, 2010). If individuals with ASD have impairments in action understanding (e.g., Iacoboni & Dapretto, 2006; Zalla, Labruyere, Clement, & Georgieff, 2010) that disrupt their ability to predict others' actions, one may expect individuals with ASD to profit less from this predictive information in the handclap condition. Finally, people with ASD may have specific problems judging audiovisual synchrony in faces because they are especially handicapped in processing socially relevant stimuli (Bebko et al., 2006; Kanner, 1943; Klin, Jones, Schultz, Volkmar, & Cohen, 2002; Riby & Hancock, 2008; Swettenham et al., 1998). Numerous studies have indeed demonstrated that individuals with ASD exhibit abnormalities in perceiving and attending facial and social stimuli (Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998; Golarai, Grill-Spector, & Reiss, 2006; Osterling & Fawson, 1994; Schultz et al., 2000). We therefore expected that people with ASD may have specific deficits judging temporal order of audiovisual speech because it is both a complex and social stimulus.

Method

Participants

Sixteen high-functioning adolescents with autism spectrum disorders were included, eleven males and five females, ranging in age between 16-22 years (mean age=19.2, SD=2.4). The clinical participants were all in residential care and recruited from *De Steiger*, a residential unit, part from *Yulius Mental Health Institution*, Dordrecht, The Netherlands, serving patients with ASD exclusively. Ten adolescents were administered the Wechsler Adult Intelligence Scale (WAIS-III) and six the Wechsler Intelligence Scale for Children (WISC-III) (see Table 1 for individual demographics per group). The severity of autistic symptoms was quantified with a checklist of the 12 DSM-IV (APA, 1994) diagnostic criteria (sub A) for 299.0 autistic disorder (see also Berger, Aerts, van Spaendonck, Cools, & Teunisse, 2003; Teunisse, Cools, Van Spaendonck, Aerts, & Berger, 2001). Based on this checklist and on the expertise of a professional clinical team, two of the participants in the ASD group met DSM-IV criteria for autistic disorder, ten for Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS) and four for Asperger's disorder.

Participants in the TD control group were recruited from Tilburg University and were non-psychiatric, eleven males (mean age=19.6 years) and five females (mean age=18.4 years), age range 18-22 years. Both groups were matched on age, gender and IQ. None of the participants had a history of serious medical, neurological or psychiatric illness (apart from ASD), seizure disorder, trauma, or use of medication affecting the nervous system.

Table 1. Individual Demographics and Just Noticeable Difference (JND) in ms per Group

Sub	*Age*	*Gender*	*Diagnosis*	*VIQ*	*PIQ*	*TIQ*	*JND Speech*	*JND Handclap*	*JND Flash*
X1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
X2	20	F	AUTISM	102	99	100	202.69	70.22	125.38
X3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
X4	18	M	PDD-NOS	89	79	83	229.21	74.27	145.96
X5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
X6	16	M	ASPERGER	107	117	114	102.09	86.54	100.18
X7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
X8	20	M	PDD-NOS	109	123	116	65.64	66.94	72.07
X9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
X10	21	M	ASPERGER	94	104	98	113.59	61.09	63.86
X11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
X12	16	F	PDD-NOS	107	102	106	110.87	81.21	127.14
X13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
X14	22	M	PDD-NOS	92	99	98	140.17	53.91	71.06
X15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
X16	24	F	ASPERGER	132	119	128	79.30	70.61	129.87

ASD Group

Sub	*Age*	*Gender*	*Diagnosis*	*VIQ*	*PIQ*	*TIQ*	*JND Speech*	*JND Handclap*	*JND Flash*
X20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
X21	18	F	-	110	108	109	92.49	75.61	65.12
X22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
X23	18	M	-	110	104	107	66.10	56.71	56.26
X24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
X25	22	M	-	90	107	96	67.50	60.91	115.98
X26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
X27	20	M	-	109	113	111	93.32	57.05	104.27
X28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
X29	18	M	-	122	111	119	96.56	65.39	65.80
X30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
X31	20	M	-	106	108	107	176.26	107.12	77.84
X32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
X33	19	M	-	103	90	97	97.65	79.89	72.56
X34	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
X35	20	M	-	111	110	111	52.36	53.13	60.71

TD Group

All reported normal or corrected-to-normal vision and hearing and were tested individually. The ASD group received gift vouchers for their participation, the TD group received course credits in return. All participants were naïve to both the experimental procedure and the purpose of the study and gave written consent prior to participating (in case of immature participants, written consent was also given by parents). The study was carried out in accordance with the ethical standards of the Declaration of Helsinki and was approved by the Medical Review Ethics Committee of the St. Elisabeth Hospital, Tilburg, The Netherlands.

Stimuli

Visual stimuli were presented on a 15-inch laptop monitor (Dell Inspiron 6000, controlled by E-Prime (Psychology Software Tools, Inc.; *http://www.pstnet.com/eprime*)) positioned on eye-level, approximately 60 cm in front of the participants. The sounds came from the laptop speakers. There were three types of stimuli: flash/beep, handclap, and speech (see Figure 1A). The flash/beep condition started with the presentation of a gray placeholder (diameter of 3.5 cm) against a dark background in the middle of the screen. After 1000-1500 ms either a 7 ms sound burst of 69 dB(A) or a white square (diameter of 1.5 cm) in the placeholders position were presented with variable stimulus onset asynchronies (sound first or flash first). The speech stimulus consisted of the pronunciation of the syllable /bi/ by a Dutch female speaker whose face was entirely visible on the monitor. In the handclap condition, a single clap of two hands was presented. The videos were presented at a rate of 25 frames/sec. The duration of the videos was 3 seconds, including a 200 ms fade-in and fade-out, and a still image (400-1100 ms) at the start. The duration of the auditory sample was 325 ms for /bi/ and 120 ms for the handclap (for more details on these stimuli see Stekelenburg & Vroomen, 2007, who originally recorded and used these stimuli). The sound pressure level of /bi/ was 63 dB(A) and 67 dB(A) for handclap (see Figure 1B). The SOA between the auditory and visual part of each stimulus stimuli varied in ten steps (±320, ±240, ±160, ±80, ±40 ms, with negative values indicating sound first). This resulted in 10 unique trials each randomly presented 16 times in two blocks of 80 trials each for each of the three stimulus conditions. The three stimulus conditions were blocked and presented in an ABCCBA design, with stimulus order counterbalanced across participants. The SOA varied randomly within each block.

Procedure

Participants were individually tested in a quiet test room (either at Tilburg University or at *Yulius/De Steiger*). The participants' task was to judge whether the sound came 'early' or 'late' relative to the visual stimulus. Responses were given by pressing one of two keys ('sound early', 'sound late') on a response box. Responses were unspeeded with emphasis on accuracy. A practice session preceding the test was given in which trials were presented with the two longest SOAs for each condition. During practice, participants received feedback ('Wrong' or 'Correct') after each trial. Practice continued until six consecutive correct answers were given. Then testing started without feedback.

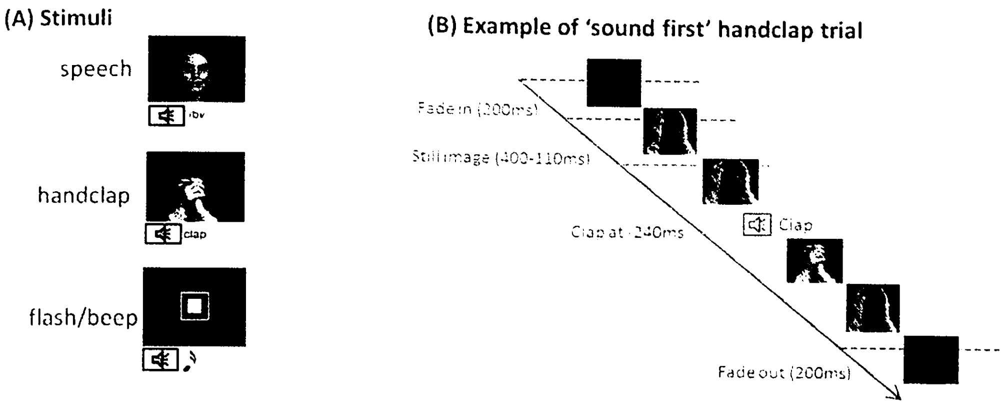


Figure 1. (A) Examples of the stimuli used in the 3 conditions; speech, handclap and flash/beep (B) Depiction a 'sound first' (the sound (handclap) is presented at -240 ms) trial in the handclap condition

Results

Trials of the practice session were excluded from analyses. The individual proportion of 'sound early' responses was calculated for each combination of stimulus condition and SOA, and then converted into equivalent Z-scores (for averaged raw data of both groups for each condition, see Figure 2). For both groups JNDs were initially computed by fitting both logistic and linear functions. The results of the logistic and linear slopes and JNDs were equivalent. The linear function provided a significantly better fit to the data of the three conditions than the logistic function for both groups, and was therefore used as the principle function. The mean and standard deviations of R^2 for the control group were .79(±.08), .81(±.08) and .85(±.11) for the three conditions (speech, handclap and flash/beep) and .76(±.14), .82(±.10) and .81(±.15) for the ASD group. For each condition, the best fitting straight line was then calculated over the ten SOAs. Two subjects (one from each group) were excluded from further analyses, because their results did not conform to a typical s-shaped function. The lines' slopes and intercepts were used to determine the just noticeable difference (JND=.675/slope) and the point of subjective simultaneity (PSS). The JND represents the smallest interval between two stimuli needed by participants to correctly judge which stimulus came first. A smaller JND thus represents good sensitivity as smaller stimulus differences are required for correctly judging temporal order. The PSS represents the average interval by which one stimulus had to lead the other for being perceived as simultaneous. The group-averaged JNDs for each condition are presented in Figure 3.

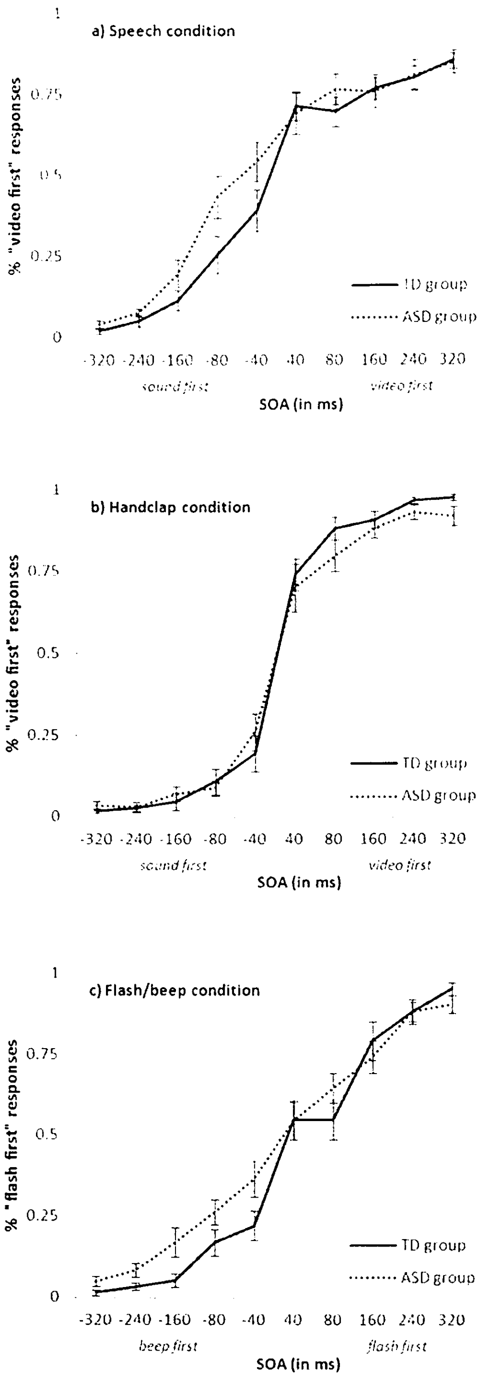


Figure 2. Averaged raw data of both the TD and ASD group for each condition ('/bi/', 'clapping hands', and 'flash-beep')

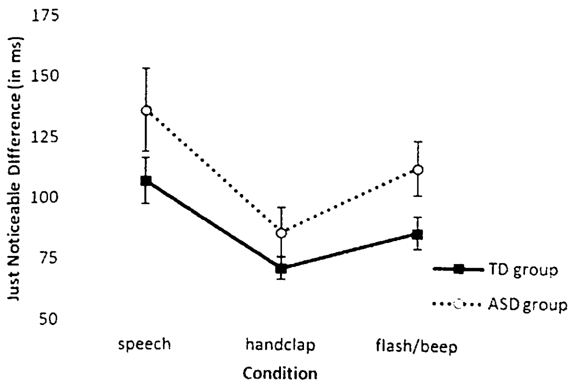


Figure 3. Group-averaged JNDs as a function of the interval between the sound and video (error bars represent one standard error of the mean)

As is clearly visible, the ASD group had overall larger JNDs than the TD group. This indicates that individuals with ASD were less sensitive to judge audiovisual temporal synchronies. This was confirmed in a 2 (Group) x 3 (Condition) ANOVA on the JNDs. There was a main effect of Group $F(1,31)=4.399$, $p<.05$, $\eta p2=.13$, indicating that, on average, the ASD group had larger JNDs than the TD group (group averages of 116.6 ms and 88.1 ms for ASD and controls, respectively). There was also a main effect on Condition $F(2,30)=12.058$, $p<.001$, $\eta p2=.29$, because sensitivity differed among the three different stimuli, while the theoretically important Group x Condition interaction was not significant, $F<1$. As also visible in Figure 3, both groups showed the smallest JNDs (best sensitivity) in the handclap condition. Independent t-tests across groups comparing the three conditions confirmed that the difference in JND (43 ms) between the speech and handclap condition, $t(31)=4.619$, $p<.001$, and the 20.4 ms difference between the flash/beep and handclap condition, $t(31)=-4.067$, $p<.001$, were significant. The difference in JND (22.3 ms) between the speech and flash/beep condition was also significant, $t(31)=2.093$, $p<.05$. To summarize, we succeeded in creating audiovisual stimuli that varied in their difficulty of judging the temporal order of their components. Individuals with ASD were, in general, less sensitive perceiving small audiovisual timing differences than controls, but they were not specifically impaired with audiovisual speech.

For completeness, similar analyses were also run on the PSSs (see Table 2). A 2 (Group) x 3 (Condition) overall ANOVA on the PSSs showed that there was no effect of Group ($F=1.137$, $p>.05$), Condition ($F=1.17$, $p>.05$), and no interaction between the two factors ($F<1$). The point at which the audiovisual stimuli were perceived to be maximally synchronous thus did not differ between group or stimuli.

Table 2. Overall Demographics and Comparison per Group, Mean Just Noticeable Difference (JND), Point of Subjective Simultaneity (PSS) in ms and Standard Deviations per Condition.

	ASD group		TD group		Comparison	
	Mean	SD	Mean	SD	*t*(30)	*p*
Age (in years)	19.2	(2.4)	19.3	(1.3)	.09	.93
Verbal IQ	106.8	(13.9)	109.0	(9.7)	.53	.60
Performal IQ	104.6	(15.4)	103.3	(8.9)	-.31	.76
Total IQ	106.2	(14.1)	106.6	(8.4)	.11	.92
Medication	*N*	*Mean daily dos.*				
Clonidine	1	.125 mg				
Paroxetine	1	20 mg				
Sertraline	2	75 mg				
Risperdal	1	1.5 mg				
Alprazolam	1	.25 mg				
Diagnoses	*N*					
Autism	2					
PDD-NOS	9					
Asperger	5					
JNDs per condition in ms						
Speech	136.2	(68.5)	107.0	(37.6)		
Handclap	86.0	(41.5)	71.3	(18.3)		
Flash/beep	112.7	(45.1)	86.0	(26.8)		
PSSs per condition in ms						
Speech	11.7	(92.4)	42.2	(77.3)		
Handclap	24.0	(64.2)	15.9	(47.5)		
Flash/beep	27.0	(90.0)	65.1	(90.7)		

Discussion

Here we examined sensitivity of audiovisual temporal asynchronies in adolescents with ASD and typically developing controls in an audiovisual TOJ task. The results showed that the ASD group had larger JNDs (= lower sensitivity) than the TD group, indicating that the ASD group had more difficulty judging audiovisual synchrony. Furthermore, we hypothesized that people with ASD might be specifically impaired when social stimuli were involved, and therefore used different stimulus classes (audiovisual speech, handclap and flash/beep). However, there was no trace of a specific impairment, as the JNDs of both groups were equally affected by the different stimuli. This thus suggests that people with ASD may suffer from a more general impairment in audiovisual temporal processing.

Our findings fit a study by Bebko et al. (2006) who showed that children with ASD had impairments in the detection of violations of temporal synchrony of audiovisual linguistic stimuli if compared to TD children and children with non-autistic developmental delays. They used a preferential looking paradigm in which the children viewed two screens displaying identical video tracks, but one offset from the other by 3 seconds, and with the single audio track that matched to only one of the displays. Even though their study showed (very small) contrasting results for non-linguistic stimuli (which can be explained by choice of paradigm and the essential difference in timing durations of the asynchrony in audiovisual stimuli, 3 seconds compared to our range of 320 ms to 40 ms), there are indications of impaired temporal sensitivity for synchrony.

Grossman et al. (2009) wanted to test whether high-functioning ASD adolescents were able to integrate AV information of meaningful, phrase-length language in a task of onset asynchrony detection. They found no significant differences between adolescents with ASD and their TD peers in accuracy of onset asynchrony detection. The authors used video clips of complete phrases, using simple, commonly occurring words. The clips were manipulated to have the video precede the corresponding audio by audio delays from 120-500 ms. Like the Bebko et al. (2006) study, the delays in this study were substantially larger compared to our study (40-320 ms). This temporal component could be an explanation for the contrasting results between the studies. As Figure 2 of our data shows, the ASD group scores near 85-95% correct on the large SOAs (at least ±320 and ±240). This percentage drops at the smaller SOAs (just like in the TD group). These results show that the ASD group is capable of judging temporal asynchrony, but their larger JNDs reveal that they need more time between the audiovisual stimuli to do so (but in a much smaller timeframe than the studies described before). A possible interpretation of these results could be that people with ASD continue to bind two stimuli as part of one event.

An extended window of temporal binding of two intermodal stimuli in people with ASD has also been proposed by Kwakye et al. (2011) and Foss-Feig et al. (2010). Results of both their flash-beep illusion and TOJ studies revealed that children with ASD have altered multisensory temporal function as they showed extended illusion ranges in performance in the multisensory tasks. For example, in the TOJ task performance gains of the children with ASD manifested themselves as improvements in accuracy and as faster responses relative to the unisensory (i.e., visual-only) baseline condition across an increased range of multisensory delays (important to mention here is that the SOAs in these studies are comparable with those in our study [a range of 0 to 500 ms]). It seems conceivable that the diminished sensitivity to temporal asynchrony we found here could result in an enlarged multisensory temporal binding window. Alternatively, though, it might also be a result of some temporal binding deficit, as proposed by Brock et al. (2002). They suggest that activity within networks of interconnected sensory areas is not as strongly correlated in ASD, resulting in disruptions in the binding of perceptual information. Kwakye et al. (2011) further speculate that it may be the case that these neural signals are not so drastically uncorrelated as to cause decoupling across regions (as initially hypothesized by Brock et al., 2002), but instead occur in such a way as to necessitate an extended temporal binding window within which two stimuli can continue to be bound as part of one event. Clearly, further research is needed for additional information on these mechanisms and theories on networks connections.

Interestingly, our results show no differences in the judgment of the audiovisual temporal order of specific stimuli between the two groups. Both groups performed best with clapping hands, followed by the artificial flash-beep, and worse with audiovisual speech. These findings concur with the results of Stekelenburg & Vroomen (2007). They used the same TOJ task (except for the artificial condition) and found that JNDs for non-speech events (clapping hands) were smaller than for speech (facial condition). This indicates that the temporal relation between audition and vision of the handclap was more precisely defined. The authors also pointed out that the clapping hands contained more anticipatory visual motion (280 ms) than the speech stimuli (160 ms), and faster transient onsets in audition and vision. They proposed that judging temporal order in audiovisual speech is particularly difficult because it contains less visual anticipatory motion and lacks fast auditory and visual transients. Apparently, predictive information can be used by individuals with ASD in this task, despite their putative impairments in action understanding.

We also hypothesized that people with ASD might have specific problems judging audiovisual temporal order in audiovisual speech because of the social component. Numerous studies reported that individuals with ASD exhibit abnormalities in facial and social stimuli (e.g., Dawson et al., 1998; Golarai et al., 2006; Osterling & Fawson, 1994; Schultz et al., 2000). However, we found no such impairments here with faces and, arguably, the handclap. An explanation might be that the participants' task in our experiment did not involve speech comprehension, face recognition, facial expression, or emotion-reading. Participants were presented a short non-word, /bi/, as pronounced by a female face and they only had to judge whether the sound came before or after the lips moved. The spoken stimuli thus had no further meaningful content, and this focus on low-level aspects of the stimulus might overshadow its social relevance. Another explanation might be more temporal, as the duration of our videos was relatively short (3 seconds) compared to other studies (e.g., Bebko et al., 2006; Dawson et al., 1998). Participants were thus exposed to much shorter fragments of faces which may ease processing load.

There are some obvious limitations in our study. Firstly, we only investigated a very specific group of high-functioning adolescents with ASD and it remains to be examined whether this can be generalized to other subtypes of ASD. Interpreting the results is also complicated by the heterogeneity of the disorder, even within each subtype. Therefore, our results may not apply to other subpopulations of ASD such as children, adults or lower-functioning people with autism. Additional research will have to consider how temporal intersensory processing varies across subpopulations and how individuals within these groups relate to those with typical development who are typically developed or to those who are both developmentally impaired and non-autistic.

Although the exact causes of our findings are speculative, they are in line with the majority of ASD studies on MSI which show that individuals with ASD have altered MSI (Bebko et al., 2006; De Gelder et al., 1991; Foxe & Molholm, 2009; Kern et al., 2007; Magnée et al., 2008; Mongillo et al., 2008; Oberman & Ramachandran, 2008; Russo et al., 2010; Smith & Bennetto, 2007), or altered multisensory temporal function (Foss-Feig et al., 2010; Kwakye et al., 2011). Further research is clearly needed to examine and characterize multisensory processes in ASD in more detail and this that may ultimately lead to a broader and better understanding and diagnosis of this disorder.

References

APA (1994). *Diagnostic and statistical manual of mental disorders* (4 ed.). Washington DC: American Psychiatric Association.

Bebko, J. M., Weiss, J. A., Demark, J. L., & Gomez, P. (2006). Discrimination of temporal synchrony in intermodal events by children with autism and children with developmental disabilities without autism. *Journal of Child Psychology and Psychiatry, 47*(1), 88-98.

Berger, H. J. C., Aerts, F., Van Spaendonck, K. P. M., Cools, A. R., & Teunisse, J. P. (2003). Central coherence and cognitive shifting in relation to social improvement in high-functioning young adults with autism. *Journal of Clinical and Experimental Neuropsychology, 25*(4), 502-511. doi: 10.1076/jcen.25.4.502.13870

Bertone, A., Mottron, L., Jelenic, P., & Faubert, J. (2005). Enhanced and diminished visuo-spatial information processing in autism depends on stimulus complexity. *Brain, 128*, 2430-2441.

Brandwein, A. B., Foxe, J. J., Butler, J. S., Russo, N. N., Altschuler, T. S., Gomes, H., & Molholm, S. (2012). The development of multisensory integration in high-functioning autism: High-density electrical mapping and psychophysical measures reveal impairments in the processing of audiovisual inputs. *Cerebral cortex Advance Access published May 24, 2012*. doi: 10.1093/cercor/bhs109

Brock, J., Brown, C. C., Boucher, J., & Rippon, G. (2002). The temporal binding deficit hypothesis of autism. *Development and Psychopathology, 14*(2), 209-224.

Courchesne, E., & Pierce, K. (2005). Why the frontal cortex in autism might be talking only to itself: Local over-connectivity but long-distance disconnection. *Current Opinion in Neurobiology, 15*(2), 225-230. doi: 10.1016/j.conb.2005.03.001

Crane, L., Goddard, L., & Pring, L. (2009). Sensory processing in adults with autism spectrum disorders. *Autism, 13*(3), 215-228. doi: 10.1177/1362361309103794

Dawson, G., Meltzoff, A. N., Osterling, J., Rinaldi, J., & Brown, E. (1998). Children with autism fail to orient to naturally occuring social stimuli. *Journal of Autism and Developmental Disorders, 28*(6), 479-485.

De Gelder, B., Vroomen, J., & Van der Heide, L. (1991). Face recognition and lip-reading in autism. *European Journal of Cognitive Psychology, 3*(69-86).

Dixon, N. F., & Spitz, L. (1980). The detection of auditory visual desynchrony. *Perception, 9*(6), 719-721. doi: 10.1068/p090719

Foss-Feig, J. H., Kwakye, L. D., Cascio, C. J., Burnette, C. P., Kadivar, H., Stone, W. L., & Wallace, M. T. (2010). An extended multisensory temporal binding window in autism spectrum disorders. *Experimental Brain Research, 203*(2), 381-389. doi: 10.1007/s00221-010-2240-4

Foxe, J. J., & Molholm, S. (2009). Ten years at the multisensory forum: Musings on the evolution of a field. *Brain Topography, 21*, 149-154.

Frith, U. (1989). *Autism: Explaining the enigma*. Malden, MA: Blackwell Publishing.

Golarai, G., Grill-Spector, K., & Reiss, A. L. (2006). Autism and the development of face processing. *Clinical Neuroscience Research, 6*, 145-160.

Grossman, R. B., Schneps, M. H., & Tager-Flusberg, H. (2009). Slipped lips: Onset asynchrony detection of auditory-visual language in autism. *Journal of Child Psychology and Psychiatry, 50*(4), 491-497.

Happé , F. (1999). Autism: Cognitive deficit or cognitive style? *Trends in Cognitive Sciences, 3*(6), 216-222. doi: 10.1016/s1364-6613(99)01318-2

Happé, F. (2005). The weak central coherence account of autism. In Volkar, Paul, Klin & Cohen (Eds.), *Handbook of autism and pervasive developmental disorders* (3rd ed., Vol. 1: Diagnosis, developmental, neurobiology, and behavior, pp. 640-649). New York: John Wiley & Sons.

Iacoboni, M., & Dapretto, M. (2006). The mirror neuron system and the consequences of its dysfunction. *Nature Reviews Neuroscience, 7*(12), 942-951. doi: 10.1038/nrn2024

Iarocci, G., & McDonald, J. (2006). Sensory integration and the perceptual experience of persons with Autism. *Journal of Autism and Developmental Disorders, 36*(1), 77-89.

Kanner, L. (1943). Autistic disturbances of affective content. *Nervous Child, 2*, 217-250.

Keane, B. P., Rosenthal, O., Chun, N. H., & Shams, L. (2010). Audiovisual integration in high functioning adults with autism. *Research in Autism Spectrum Disorders, 4*(2), 276-289. doi: 10.1016/j.rasd.2009.09.015

Keetels, M., & Vroomen, J. (2012). Perception of synchrony between the senses. In M. M. Murray & M. T. Wallace (Eds.), *Frontiers in the neural basis of multisensory processes* (pp. 147-177). London: Taylor & Francis Group.

Kern, J. K., Trivedi, M. H., Grannemann, B. D., Garver, C. R., Johnson, D. G., Andrews, A. A., . . . Schroeder, J. L. (2007). Sensory correlations in autism. *Autism, 11*(2), 123-134. doi: 10.1177/1362361307075702

Klin, A., Jones, W., Schultz, R., Volkmar, F., & Cohen, D. (2002). Visual fixation patterns during viewing of naturalistic social situations as predictors of social competence in individuals with autism. *Archives of General Psychiatry, 59*(9), 809-816. doi: 10.1001/archpsyc.59.9.809

Kwakye, L. D., Foss-Feig, J. H., Cascio, C. J., Stone, W. L., & Wallace, M. T. (2011). Altered auditory and multisensory temporal processing in autism spectrum disorders. *Frontiers in integrative neuroscience, 4*, 129.

Magnée, M. J., De Gelder, B., Van Engeland, H., & Kemner, C. (2008). Audiovisual speech integration in pervasive developmental disorders: Evidence from event-related potentials. *Journal of Child Psychology and Psychiatry, 49*(9), 995-1000.

Mongillo, E. A., Irwin, J. R., Whalen, D. H., Klaiman, C., Carter, A. S., & Schultz, R. T. (2008). Audiovisual processing in children with and without Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders, 38*, 1349-1358.

Mottron, L., & Burack, J. (2001). Enhanced perceptual functioning in the development of autism. In C. Y. Burack & Zelazo (Eds.), *The development of autism: Perspectives from theory and reserach* (pp. 131-148). Mahwah, NJ: Erlbaum.

O'Neill, M., & Jones, R. S. P. (1997). Sensory-perceptual abnormalities in autism: A case for more research? *Journal of Autism and Developmental Disorders, 27*, 283-293.

Oberman, L. M., & Ramachandran, V. S. (2008). Preliminary evidence for deficits in multisensory integration in autism spectrum disorders: The mirror neuron hypothesis. *Social Neuroscience, 3*(3-4), 348-355.

Osterling, J., & Fawson, G. (1994). Early recognition of children with autism: A study of first birthday home videotapes. *Journal of Autism and developmental disorders, 24*, 247-257.

Pöppel, E. (1997). A hierarchical model of temporal perception. *Trends in Cognitive Sciences, 1*(2), 56-61.

Radeau, M. (1994). Auditory-visual spatial interactionand modularity. *Cahiers de Psychologie Cognitive-Current Psychology of Cognition, 13*(1), 3-51.

Riby, D. M., & Hancock, P. J. B. (2008). Viewing it differently: Social scene perception in Williams syndrome and Autism. *Neuropsychologia, 46*(11), 2855-2860. doi: 10.1016/j.neuropsychologia.2008.05.003

Russo, N., Foxe, J. J., Brandwein, A. B., Altschuler, T., Gomes, H., & Molholm, S. (2010). Multisensory processing in children with autism: High-density electrical mapping of auditory somatosensory integration. *Autism Research, 3*(5), 253-267. doi: 10.1002/aur.152

Scheier, C. R., Nijhawan, R., & Shimojo, S. (1999). Sounds alters visual temporal resolution. *Investigative Ophthalmology & Visual Science, 40*, 4169.

Schultz, R. T., Gauthier, I., Klin, A., Fulbright, R. K., Anderson, A. W., Volkmar, F., . . . Gore, J. C. (2000). Abnormal ventral temporal cortical activity during face discrimination among individuals with autism and Asperger syndrome. *Archives of General Psychiatry, 57*, 331-340.

Senkowski, D., Schneider, T. R., Foxe, J. J., & Engel, A. K. (2008). Crossmodal binding through neural coherence: Implications for multisensory processing. *Trends in Neurosciences, 31*, 401-409.

Shams, L., Kamitani, Y., & Shimojo, S. (2000). Illusions - What you see is what you hear. *Nature, 408*(6814), 788-788. doi: 10.1038/35048669

Smith, E. G., & Bennetto, L. (2007). Audiovisual speech integration and lipreading in autism. *Journal of Child Psychology and Psychiatry, 48*(8), 813-821.

Stein, B., & Meredith, M. A. (1993). *The merging of the senses*. Cambridge MA: The MIT Press.

Stekelenburg, J., & Vroomen, J. (2007). Neural correlates of multisensory integration of ecologically valid audiovisual events. *Journal of cognitive neuroscience, 19*(12), 1-10.

Swettenham, J., Baron-Cohen, S., Charman, T., Cox, A., Baird, G., Drew, A., . . . Wheelwright, S. (1998). The frequency and distribution of spontaneous attention shifts between social and nonsocial stimuli in autistic, typically developing, and nonautistic developmentally delayed infants. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 39*(5), 747-753. doi: 10.1017/s0021963098002595

Szelag, E., Kowalska, J., Galkowski, T., & Pöppel, E. (2004). Temporal processing deficits in high-functioning children with autism. *British Journal of Psychology, 95*, 269-282.

Teunisse, J. P., Cools, A. R., Van Spaendonck, K. P. M., Aerts, F., & Berger, H. J. C. (2001). Cognitive styles in high-functioning adolescents with autistic disorder. *Journal of Autism and Developmental Disorders, 31*(1), 55-66. doi: 10.1023/a:1005613730126

Van der Smagt, M. J., Van Engeland, H., & Kemner, C. (2007). Brief report: Can you see what is not there? Low-level auditory-visual integration in Autism Spectrum Disorder. *Journal of Autism and developmental disorders, 37*, 2014-2019.

Vroomen, J., & De Gelder, B. (2004). Temporal ventriloquism: Sound modulates the flash-lag effect. *Journal of Experimental Psychology: Human Perception and Performance, 30*(3), 513-518.

Vroomen, J., & Keetels, M. (2010). Perception of intersensory synchrony: A tutorial review. *Attention Perception & Psychophysics, 72*(4), 871-884. doi: 10.3758/app.72.4.871

Wallace, M. (2004). The development of multisensory integration. In G. A. Calvert, C. Spence & B. E. Stein (Eds.), *The handbook of multisensory processes* (pp. 625-642). Cambridge MA: MIT.

Welch, R. B., & Warren, D. H. (1980). Immediate percetual response to intersensory discrepancy. *Psychological Bulletin, 88*(3), 638-667.

Williams, J. H. G., Massaro, D. W., Peel, N. J., Bosseler, A., & Suddendorf, T. (2004). Visual-auditory integration during speech imitation in autism. *Research in Developmental Disabilities, 25*(6), 559-575. doi: 10.1016/j.ridd.2004.01.008

Zalla, T., Labruyere, N., Clement, A., & Georgieff, N. (2010). Predicting ensuing actions in children and adolescents with autism spectrum disorders. *Experimental Brain Research, 201*(4), 809-819. doi: 10.1007/s00221-009-2096-7

Chapter 4

Intact multisensory integration of low-level audiovisual stimuli in adolescents with ASD

De Boer-Schellekens, L.

Keetels, M.

Eussen, M.

Vroomen, J.

Neuropsychologia, accepted pending minor revisions

Abstract

Abrupt click sounds can improve the visual processing of flashes in several ways. Here, we examined this in high-functioning adolescents with Autism Spectrum Disorders (ASD) using three tasks: (1) a task where clicks improve sensitivity for visual temporal order (temporal ventriloquism); (2) a task where a click improves visual search ('pip-and-pop'), and (3) a task where a click speeds up the visual orienting to a peripheral target (clock reading). Adolescents with ASD were, compared to adolescents with typical development (TD), less sensitive in judgments of visual temporal order, but they were unimpaired in visual search and orienting. Importantly, in all tasks visual performance of the ASD group improved by the presence of clicks by at least equal amounts as in the TD group. This clearly indicates that adolescents with ASD show no generalized deficit in the multisensory integration of low-level audiovisual stimuli and/or the phasic alerting by abrupt sounds.

Introduction

Autism Spectrum Disorders (ASD) are characterized by deficits in social interactions, communication, and by restricted interests and/or repetitive behaviors (APA, 1994). In addition, sensory disturbances have been reported consistently in the clinical literature dating back to Kanner's original description of autism (Kanner, 1943). Indeed, several contemporary theories on ASD reflect the idea that sensory deficits are core symptoms of autism (Crane, Goddard, & Pring, 2009; Kern et al., 2007) that could have downstream effects on the development of the perceptual system (Bertone, Mottron, Jelenic, & Faubert, 2005; Mottron & Burack, 2001). To create a unified percept of the world, the brain has to synthesize a mix of sensory information into one coherent multisensory percept. This sensory synthesis is a constantly occurring phenomenon that shapes our view of the world and it is crucial for everyday social and adaptive behavior (Wallace, 2004). Deficits in (multi)sensory processing might lead to aberrant social and adaptive behavior and interaction as known in ASD.

There is indeed evidence that people with ASD have impairments in (multi)sensory processing. One piece of evidence comes from studies on the Multisensory Integration (MSI) of speech and emotions as perceived from the face and the voice (Bebko, Weiss, Demark, & Gomez, 2006; Charbonneau et al., 2013; De Gelder, Vroomen, & Van der Heide, 1991; Magnée, De Gelder, Van Engeland, & Kemner, 2008; Megnin et al., 2012; Mongillo et al., 2008; Smith & Bennetto, 2007). These studies suggest that people with ASD have problems with audiovisual integration of social and emotional stimuli that could account for the atypical social behavior of individuals with ASD. Other studies on MSI of lower-level information like clicks and flashes, though, show opposite results (Foss-Feig et al., 2010; Grossman, Schneps, & Tager-Flusberg, 2009; Keane, Rosenthal, Chun, & Shams, 2010; Kwakye, Foss-Feig, Cascio, Stone, & Wallace, 2011; Magnée, Oranje, Van Engeland, Kahn, & Kemner, 2009; Mongillo et al., 2008; Van der Smagt, Van Engeland, & Kemner, 2007). This dichotomy between the processing of complex and lower-level stimuli may be in line with the conceptualization of autism as a selective disorder of complex information processing (Minshew, Sweeney, & Luna, 2002). However, a recent study by Brandwein et al. (2012) assessed the integrity of basic audiovisual integration by recording high-density electrophysiology from high-functioning children with ASD while the children performed a simple audiovisual reaction time task. The authors found that children with ASD showed considerably less behavioral facilitation to multisensory inputs. Two other recent studies by Foss-Feig et al. (2010) and Kwakye et al. (2011) showed that, although children with ASD are well able to integrate audiovisual information, they do have an altered multisensory temporal binding window. For example, the Kwakye et al. (2011) study reported an extended window of temporal integration in children with ASD using Temporal Order Judgment (TOJ) tasks with visual, auditory, and audiovisual stimuli. The authors reported no differences in sensitivity for visual temporal order, but thresholds were higher in ASD on the auditory TOJ task. In the multisensory TOJ task, the authors relied on the phenomenon known as 'temporal ventriloquism' (Scheier, Nijhawan, & Shimojo, 1999), where click sounds improve sensitivity for visual temporal order if the clicks are presented within a certain time window. Children with ASD showed performance improvements over a wider range of temporal intervals than TD children, which is in line with the idea that children with ASD have a wider temporal window of MSI that could serve as a possible explanation for the observed differences in MSI in people with ASD.

A recent study by De Boer-Schellekens, Eussen & Vroomen (2013) also examined whether people with ASD suffer from intersensory temporal deficits that may underlie other impairments in MSI. An audiovisual TOJ task was used to study sensitivity of audiovisual temporal asynchronies in adolescents with ASD on three kinds of stimuli that are known to differ on a number of potentially relevant dimensions (a single flash/beep, the video of a handclap, or the video of a face articulating a syllable). This allowed the authors to examine whether adolescents with ASD suffered from a general or a more specific impairment in audiovisual temporal processing. The asynchrony between the audio and video was varied and participants judged whether the auditory stimulus came 'early' or 'late' with respect to the video. Results showed that, compared to TD controls, individuals with ASD were generally less sensitive in judgments of audiovisual temporal order, but there was no specific impairment with social stimuli (i.e., the face/speech stimulus), thus indicating that people with ASD may suffer from a more general impairment in audiovisual temporal processing.

It has also been reported that people with ASD may have problems in visual attention, especially with the (dis)engagement and orienting of attention (e.g., Courchesne et al., 1994; Harris, Courchesne, Townsend, Carper, & Lord, 1999; Landry & Bryson, 2004; Renner, Klinger, & Klinger, 2006; see Simmons et al., 2009 for a review ; Van der Geest, Kemner, Camfferman, Verbaten, & Van Engeland, 2001; Wainwright & Brown, 1996; Wainwright-Sharp & Bryson, 1993). These attentional deficits may also be related to poor judgments of visual temporal order, as has been suggested for dyslexia (Hari & Renvall, 2001).

In the present study we contribute to the ongoing debate on MSI and visual attention in ASD by examining the performance of adolescents with ASD on three different tasks. First, we examined MSI using a phenomenon known as 'temporal ventriloquism'. The basic phenomenon is that an abrupt click can attract the perceived timing of a flash in time. A sound before a flash (at 100 ms) can make the flash appear earlier, and a sound after the flash (also at 100 ms) can make the flash appear later (Morein-Zamir, Soto-Faraco, & Kingstone, 2003; Scheier et al., 1999; Stekelenburg & Vroomen, 2005; Vroomen & De Gelder, 2004; Vroomen & Keetels, 2006). One way to demonstrate this is by means of a visual TOJ task where participants judge which of two flashes appeared first. When two click sounds are 'sandwiched', one before the first flash and one after the second flash, sensitivity to visual temporal order improves, presumably because the apparent stimulus onset asynchrony (SOA) between the two flashes is increased (see Figure 1A). The question we addressed here is whether equal amounts of temporal ventriloquism can be observed at various audiovisual SOAs in adolescents with ASD if compared to a TD control group. If people with ASD have difficulties with MSI, they should have a *diminished* temporal ventriloquist effect because sounds are not well-integrated with flashes. Alternatively, if they have an enlarged 'window of temporal integration' (Foss-Feig et al., 2010; Kwakye et al., 2011), one may observe improvements by sounds at atypical large SOAs.

Second, we examined MSI with the 'pip-and-pop' task as introduced by Van der Burg, Olivers, Bronkhorst, & Theeuwes (2008). In this task, a visual target (a horizontal or vertical line) is embedded in a cluttered display of distracters (oblique lines). The targets and distracters change, on randomly determined times, color from green-to-red or red-to-green. The search time can be drastically improved if a 'pip'-sound is synchronized with the color-change of the target: the 'pip' then makes the target 'pop-out'. We used this task to examine whether the 'pip' improves visual search time of adolescents with ASD as it does in adolescents with typical development. We hypothesized that if people with ASD have problems with the disengagement of attention from the current fixation (e.g., Landry & Bryson, 2004), one expects them in the tone-absent condition (serial search) to have longer search times than the TD group. The slope of their search-time-per-item function should then also be steeper as compared to the TD group (see also Romani, Tsouknida, Di Betta, & Olson, 2011; Sireteanu et al., 2008; Vidyasagar & Pammer, 1999). In the sound-present condition, though, the 'pip' can make the target 'pop-out' (parallel search), and search time may become independent of the set size of the distracters. If MSI is unimpaired in ASD, then ultimately a single 'pip' might compensate for their visual attention deficit. It should be noted that the 'pip-and-pop' task uses a cluttered visual display where the target and many distracters change color at approximately the same time. Extracting audiovisual synchrony between the sound and the color change of the target seems like a key requisite that is likely challenged in this task. To the extent that the adolescents with ASD have problems extracting audiovisual synchrony, one would expect them to profit less from sound because the sound might be wrongly combined with a change of a distracter rather than the target.

The third task was motivated by the idea that poor judgments of temporal order might be a result of impairments in the shift or disengagement of visual attention (e.g., Courchesne et al., 1994; Harris et al., 1999; Landry & Bryson, 2004; Wainwright-Sharp & Bryson, 1993). We used a 'digital clock reading' task that allowed us to obtain insight into the orienting of attention (Keetels & Vroomen, 2011). In this task, participants viewed two streams of digits in rapid serial visual representation (RSVP), one on the left, the other on the right of fixation. After a variable time, one of the streams was cued by a placeholder turning red (an exogenous cue). Participants were asked to report the digit that they saw in the target stream at the time the placeholder turned red. The time it takes to overtly shift attention towards the stream and to read out the target digit can be estimated from the delay between the actual digit and the reported digit. This delay is referred to as the 'visual latency'. The task contained a silent condition and two sound conditions where a short click from central location was presented either ~100 ms or ~200 ms before the cue. If people with ASD have problems with the shifting and/or disengagement of visual attention, one might expect them to have slower visual latencies than adolescents with TD in a silent condition. Furthermore, click sounds at ~200 or ~100 ms before the presentation of the cue/target have been demonstrated to improve visual latency for various reasons: A click may enhance detection of the cue, and/or it may improve the disengagement from fixation, speed-up the shift of attention, or the click may release backward masking so that the visual stimulus with which the click is synchronized becomes more visible (Chen & Spence, 2011; Vroomen & De Gelder, 2000; Vroomen & Keetels, 2009). If alerting by sound is unimpaired in people with ASD, we expected them to profit from clicks as the TD controls.

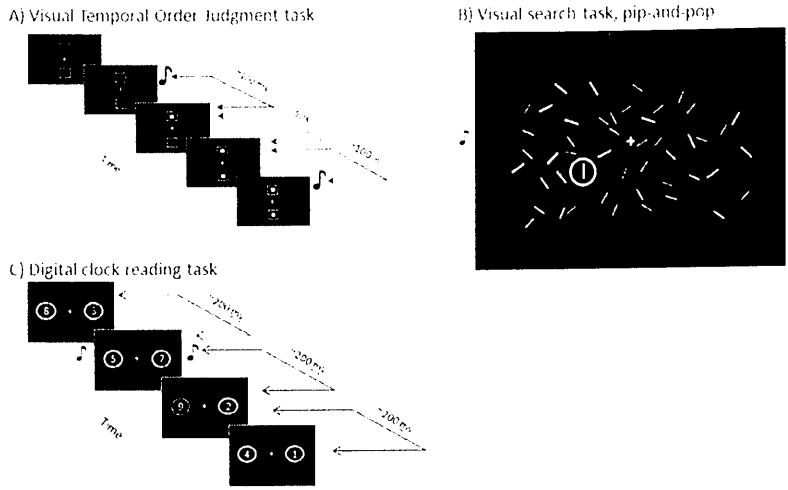


Figure 1. Set-up and examples of the experiments. (A) Depiction of a trial in the visual temporal order judgment task for the ~100 ms audiovisual delay condition. (B) Example of the visual search display with set size 48 (the target is outlined). (C) Depiction of a trial in the digital clock reading task for a ~200 ms sound before cue condition

Methods

Participants

A group of 35 adolescents/young adults with ASD and 40 with typical development (TD) participated in this study. All clinical participants were recruited from *De Steiger*, a residential unit, part from *Yulius Mental Health Institution*, Dordrecht, The Netherlands, serving patients with ASD exclusively. The TD group was recruited from educational institutions nearby Tilburg, The Netherlands. Participants were eligible for this study if they did not have a history of psychiatric disorders or psychiatric treatment. Groups were matched on gender and age. None of the participants had a history of serious medical, neurological, or psychiatric illness (apart from ASD) or trauma capitis. Eligibility criteria for all adolescents were; (a) age between 15-24; (b) Total IQ above 80; and (c) normal or corrected to normal hearing and vision. All participants (except for three participants in the TD group) were administered the Wechsler Adult Intelligence Scale (WAIS-III) or the Wechsler Intelligence Scale for Children (WISC-III) (see Tables 1 and 2 for participants' characteristics per experiment). All participants in the ASD group had prior clinical diagnoses of ASD confirmed by a licensed clinical psychologist or psychiatrist. For 16 adolescents the severity of autistic symptoms was quantified with a checklist of the 12 DSM-IV TR (APA, 1994) diagnostic criteria (sub A) for 299.0 autistic disorder (see also Berger, Aerts, Van Spaendonck, Cools, & Teunisse, 2003; Teunisse, Cools, Van Spaendonck, Aerts, & Berger, 2001). For 14 adolescents diagnosis was supported by scores on the Social Responsiveness Scale (SRS; Constantino & Gruber, 2005). A cut-off score of 75 on the SRS is associated with a sensitivity of .85 and a specificity of .75 for any autism spectrum condition (Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), Asperger Syndrome or Autistic Disorder) by expert clinician diagnosis. In our sample, 92% scored above this threshold. Based on these criteria, seven of the participants in the ASD group met DSM-IV TR criteria for autistic disorder, 18 for PDD-NOS and 10 for Asperger's disorder. All adolescents were tested individually and received compensation for their participation. A group of 32 adolescents (16 with ASD, 16 with TD) only participated in the visual TOJ task. The data of one participant in the TD group was excluded from analyses because of overall erratic results. Participants were all naïve to both the experimental procedures and the purpose of the study and gave written consent prior to participating (in case of immature participants, written consent was also given by parents). The study was carried out in accordance with the ethical standards of the Declaration of Helsinki and was approved by the Medical Review Ethics Committee of the St. Elisabeth Hospital, Tilburg, The Netherlands.

Table 1. Participant Characteristics of Experiment 1: Visual Temporal Order Judgment task

	ASD group		TD group		Comparison	
	Mean	SD	Mean	SD	*t*	*p*
Age (in years)	18.8	2.1	18.8	1.3	.009	.99
Verbal IQ	104.6	16.3	109.4	10.0	1.51	.14
Performal IQ	102.6	15.4	106.1	11.0	1.13	.26
Total IQ	103.2	14.6	107.9	9.1	1.66	.11
SRS score	88.7	28.6				
Medication	*N*	*Mean daily dos.*				
Abilify	1	15 mg				
Frazolan	1	100 mg				
Lexapro	1	10 mg				
Dipiperon	1	60 mg				
Clomipramine	1	75 mg				
Sertraline	3	42 mg				
Risperdal	3	1 mg				
Pantozol	1	20 mg				
Clonidine	1	.125 mg				
Paroxetine	1	.20 mg				
Alprazolam	1	.25 mg				
Diagnoses	*N*					
Autism	7					
PDD-NOS	18					
Asperger	19					

Table 2. Participant Characteristics of Experiment 2 ('Pip-and-Pop' Task) and 3 (Digital Clock Reading Task)

	ASD group		TD group		Comparison	
	Mean	SD	Mean	SD	*t*	*p*
Age (in years)	18.2	2.1	18.4	1.1	-.029	.98
Verbal IQ	106.9	16.3	109.4	10.6	.66	.51
Performal IQ	102.1	17.4	109.8	12.9	1.56	.13
Total IQ	103.7	14.6	109.8	10.6	1.52	.14
SRS score	88.7	28.6				
Medication	*N*	*Mean daily dos.*				
Abilify	1	15 mg				
Lexapro	1	10 mg				
Dipiperon	1	60 mg				
Clomipramine	1	75 mg				
Sertraline	1	50 mg				
Risperdal	2	1 mg				
Diagnoses	*N*					
Autism	5					
PDD-NOS	8					
Asperger	6					

General procedure

Participants were tested individually, either at Tilburg University or at *Yulius/De Steiger*. The visual stimuli were presented on a 15-inch, 60 Hz laptop monitor (Dell Inspiron 6000), controlled by E-Prime 1.2 (Psychology Software Tools, Inc.; *http://www.pstnet.com/eprime*). Auditory stimuli were presented through a headphone (in the visual TOJ tasks) or the speakers of the laptop (in the 'pip-and-pop' task and the digital clock reading task). Participants were seated approximately 60 cm in front of the laptop screen with head movements precluded by a chin-rest. Responses were recorded via a serial response box or keyboard. A verbal instruction and practice session preceding the tests was given for each experiment.

Stimuli and design

Visual Temporal Order Judgment task with clicks

Stimuli and procedures were similar to previous studies (e.g., Vroomen & Keetels, 2006) and were optimized to examine a temporal ventriloquist effect over an extended range of sound-light intervals. Visual stimuli consisted of two white squares (1.2° visual angle) presented in two gray placeholders (2.8° visual angle) against a dark background at variable SOAs. The squares were presented at 2.4 degrees above and below a central fixation cross (see Figure 1A). The auditory stimuli consisted of two 2 ms sounds extracted from white noise that sounded as click sounds. The clicks were presented at 71 dB(A) and presented through a headphone. A small red cross served as a fixation point and was placed at eye-level, at central location, approximately 60 cm in front of the participant. There were two within-subject factors: sound presence (five levels: visual-only, and four sound conditions with SOAs between the sound and flash of ~0 ms, ~100 ms, ~200 ms, or ~300 ms) and the visual stimulus onset asynchrony (SOA) between the upper and lower square. For 16 participants the SOA varied between ±133 ms, ±100 ms, ±67 ms, ±33 ms (with negative values indicating that the lower visual stimulus was presented first), resulting in 40 unique trials each randomly presented 16 times in four blocks of 10 trials each. For the other participants SOAs varied between ±100 ms, ±67 ms, ±50, ±33 and ±16 ms. This resulted in 50 unique trials, each randomly presented 12 times in four blocks of 150 trials each. Within blocks, all combinations of SOA and sound presence varied randomly. The experiment lasted ~30 minutes.

A red fixation light was illuminated at the beginning of the experiment and participants were instructed to maintain fixation during testing. Each trial consisted of the onset of the first visual stimulus and, after a variable SOA, the second visual stimulus was presented. The two squares remained on the screen until a response was made. Sounds (if present) were presented at various audiovisual lags, depending on condition. Participants were instructed not to pay attention to the sounds, as they did not predict in any sense which stimulus appeared first. Participants judged whether the upper or the lower square had appeared first by pressing a corresponding key on a response box. The next trial started 800 ms after a response was given. Responses were unspeeded with emphasize on accuracy. A practice session preceded the test with the two longest SOAs for each condition. During practice, participants received feedback ('Wrong' or 'Correct') after each trial. Practice continued until six consecutive correct answers were given. Then testing started without feedback.

'Pip-and-Pop' task

The stimuli were made as in the Van der Burg et al. (2008) study. The auditory stimulus was a short white noise click of 68 ms presented at 74 dB(A) through the speakers of the laptop. The visual search displays consisted of 18, 24, 36 or 48 red (20 cd/m^{-2}) and green (11 cd/m^{-2}) line segments (length .88° visual angle) against a dark background (<0.05 cd/m^{-2}). The initial color (red or green) was randomly determined for each item. The lines were randomly placed in an invisible 10 * 10 grid (10.5° * 6.5°) centered on a white central fixation cross, with the constraint that the target was never presented at the four central positions, to avoid immediate detection. The target was a horizontal or vertical line, while for distracters line orientation deviated randomly by plus or minus 26.5° from horizontal or vertical (see Figure 1B). The distracters changed color (from red-to-green or vice versa) every 50 ms, 100 ms, or 150 ms. The number of distracters that changed simultaneously during a trial varied for the different set sizes; in set size 18, one, two or three distracters changed simultaneously, in set size 24, one, two or four distracters, in set size 36, one, three or six distracters and in set size 48 it was one, four or seven distracters. The target changed color every 500 or 1000 ms, and always changed alone. The target change was always preceded by a 150 ms-interval and followed by a 100 ms-interval during which distracter did not change color. During the first 500 ms of a trial, the target did not change color.

There were two within-subjects factors: Set size (18 or 36, 24 or 48) and Sound (present or absent). These factors were varied randomly across trials. Target orientation was balanced and randomly mixed. There were two versions of the experiment in which 2 set sizes were presented within the same task (set size 18 and 36, and set size 24 and 48). Participant completed both versions, with task order (set size 18-36 or 24-48) counterbalanced across participants. Each task consisted of one block of 80 experimental trials, in which each of the four unique conditions was presented 20 times. The experiment lasted ~20 minutes in total.

At the beginning of each trial, a white fixation cross was illuminated in the center of the screen. Participants were asked to remain focused on the fixation cross. After 150-500 ms the display with target and distracters appeared at the screen. Both target and distracters were present at the beginning of each trial. In the sound-present condition, a change in the color of the target was accompanied by a click sound. The search display was presented until the participants made a response. Participants were instructed to search for the target and to press one of two buttons on a response box corresponding with the target orientation '–' or '|' as fast and accurately as possible. All participants were explicitly told that sounds were synced with a color-change of the target, and that they thus could benefit from the sound. They were free to use their own search strategy that enabled them to detect the target as fast as possible. To encourage that participants reacted as fast and as accurately as possibly throughout the whole experiment, feedback about accuracy and search time was given after each trial. Overall scores were given at the end of the experiment.

Digital Clock Reading task

The visual stimulus consisted of two circular placeholders arranged horizontally at 7.1 degrees of visual angle from a central fixation cross (see Figure 1C). Within each circle, a unique single digit was displayed in RSVP mode changing every 200 ms (5 Hz). Each of the two digits changed randomly and the two digits were never the same. The auditory stimulus consisted of a 30 ms white noise burst presented at 84 dB via the laptop speakers so that the sound appeared to emanate from the center.

At the beginning of a trial, a fixation cross appeared together with the two circular placeholders in which the RSVP streams were presented. After a randomly selected time (between 1800 and 3200 ms), one of the circular placeholders turned red for the duration of one digit (i.e., 200 ms) thus indicating which stream (left or right) contained the target digit. After the cue had disappeared, the digits kept streaming up to four digits after the cue so that the target could not be estimated from the final digit in the stream. The sound, if present, was presented ~100 ms or ~200 ms before the cue. The participant's task was to report the digit that he/she saw in the cued stream at the time the placeholder turned red. Answers were given by pressing a numeric key via a standard keyboard.

There were two within-subjects factors: sound presence (silent, or sound present at ~100 or ~ 200 ms before the cue), and target location (left or right from fixation). These two factors varied randomly across trials. The whole test consisted of two blocks of 60 experimental trials each, in which each of the six unique conditions was presented 20 times, lasting ~15 minutes in total.

Results

Visual Temporal Order Judgment task with click sounds

To obtain a measure of sensitivity of visual temporal order, data were analyzed as in previous studies by fitting a logistic function on the raw data (e.g., Vroomen & Keetels, 2006)[1]. Trials of the practice session were excluded from analyses. The individual proportion of 'upper light first' responses for each combination of stimulus condition and SOA were converted into equivalent Z-scores, and for each condition, the best fitting straight line was then calculated over the SOAs. The data of five subjects (two from the ASD group and three of the TD group) were excluded from further analyses, because (1) their results did not conform to a typical s-shaped function, or (2) did not complete the task due to a lack of test time. The lines' slopes were used to determine the just noticeable difference (JND=.675/slope in which a Z-score of .675 corresponds to a *p*-value of .75). The JND represents the smallest interval between two stimuli needed by participants to correctly judge which stimulus came first on 75% of the trials. A small JND thus reflects sensitivity being good, as smaller stimulus differences are required to correctly judge temporal order. The group averaged proportion of 'upper light first'-responses are presented in Figure 2 and the corresponding JNDs for each condition are presented in Figure 3. As is clearly visible, the ASD group had larger JNDs (they were less sensitive) in the visual-only condition than the TD group, but the presence of the two click sounds drastically improved their sensitivity up to the level of TD group. The TD control group also benefitted from sounds, but their multisensory enhancement was actually smaller than that of the ASD group.

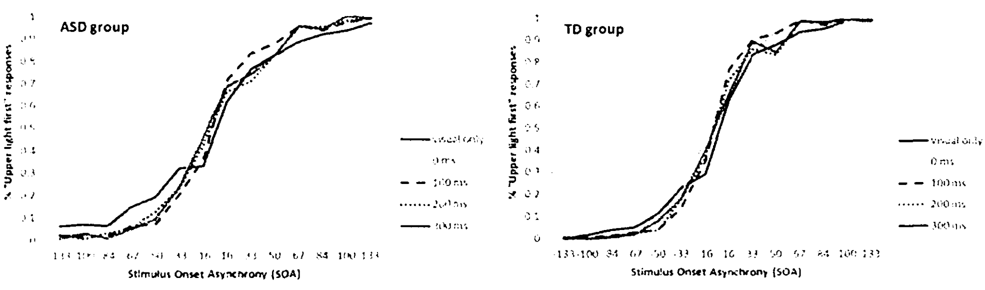


Figure 2. Group averaged proportion of 'upper light first' responses in the visual TOJ task

[1] For both groups JNDs were fitted by the linear function. The mean and standard deviations of R^2 for the TD *control group were* .88(±.07), .91(±.03), .90(±.05), .91(±.04) and .91(±.04) for the five conditions (visual-only, 0, 100, 200 and 300 ms audiovisual delay) and .83(±.11), .87(±.06), .88(±.06), .86(±.07) and .88(±.06) for the ASD group.

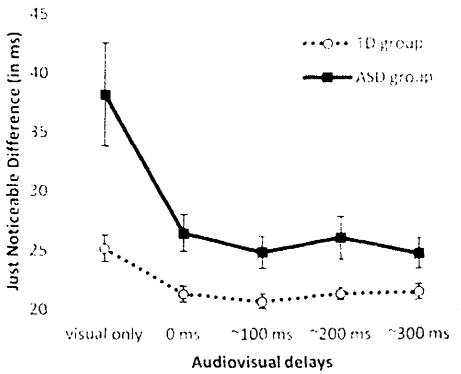


Figure 3. Group-averaged JNDs as a function of the interval between the sound and the flash (error bars represent one standard error of the mean)

This was confirmed in a 2 (Group) x 2 (SOA) x 5 (Condition) ANOVA on the JNDs. There was a main effect of Group $F(1,68)=12.501$, $p=.001$, $\eta p2=.16$, indicating that, on average, the ASD group had larger JNDs than the TD group. There was also a main effect of Condition $F(4,65)=15.788$, $p<.001$, $\eta p2=.20$, because for both groups sensitivity improved when sounds were present rather than absent (a temporal ventriloquist effect). As Figure 3 shows, the drop in JNDs in the sound conditions was larger for the ASD group than for the TD group, indicating that the ASD group profited more from sound. This difference was reflected in an interaction between Group and Condition $F(4,65)=4.616$, $p=.001$, $\eta p2=.07$. Because the interaction seemed to be mainly caused by the difference in the visual-only condition, we also ran a 2 (Group) x 2 (SOA) x 4 (Condition) ANOVA on the JNDs in the sound-present conditions. In this analysis, the Group effect remained significant $F(1,68)=11.083$, $p=.001$, $\eta p2=.15$, indicating that the TD group was also in the sound-present conditions more sensitive to visual temporal order than the ASD group. The Group x Condition interaction ($F<1$) was not significant anymore, thus indicating that the ASD group had a similar window of MSI as the TD group.

For completeness, similar analyses were also run on the point at which the two flashes were perceived to be subjectively simultaneous (the PSS). A 2 (Group) x 2 (SOA) x 5 (Condition) overall ANOVA on the PSSs showed that there were no main effects of Group ($F<1$), Condition ($F(4,65)=1.791$, $p=.11$), and no interaction between the two factors ($F(4,65)=1.791$, $p=.13$), indicating that the point at which the audiovisual stimuli were perceived to be maximally synchronous did not differ between groups.

'Pip-and-pop' task

The data of the practice session and erroneous responses were excluded from analyses. Furthermore, seven participants (one from the TD group, six of the ASD group) were excluded from analyses because participants (1) had difficulties with the task (three adolescents in the ASD group kept asking for instruction during the task and could not concentrate), (2) did not complete both test sessions (two in the ASD group) and (3) had a large percentage of false responses (one in the TD group (17% of all trials) and one in the ASD group (32.5% of all trials)). After removal, the overall error rate was low (2.36% for the TD group and 2.36% for the ASD group), and did not differ significantly between groups, $t(33)=.004$, $p=.997$. No further analyses were therefore performed on error rates.

Search time was measured from the onset of the first display until the response to the target. The averaged search times for each condition are presented in Figure 4. An overall repeated measures ANOVA was conducted with Group as between-subject factors and Set size (18, 24, 36 or 48 items) and Sound (absent or present) as within-subject factors. There was a hint that individuals with ASD had actually faster overall search times than TD individuals, but the Group effect was not significant, $F(1,34)=2.274$, $p=.14$ (mean search time of 4,358 ms for the ASD group and 5,276 ms for the TD group). As expected, average search time of both groups increased with Set size $F(3,32)=68.25$, $p<.01$, $\eta p2=.81$ (mean search time of 2,520 ms for set size 18, 3,777 ms for set size 24, 5,485 ms for set size 36 and 7,488 ms for set size 48), and the search time of trials with sound was faster than without Sound $F(1,34)=5.83$, $p=.021$, $\eta p2=.15$ (mean search time of 5,135 ms for the sound absent conditions vs. 4,500 ms for the sound present conditions), thus showing the basic 'pip-and-pop' effect. There was no interaction between Set size and Group, $F(3,32)=1.14$, $p=.33$, indicating that the search-time-per-item did not differ between groups (ASD group; 138 ms/item, TD group 168 ms/item). There was a significant interaction between Sound and Set size, $F(3,32)=5.22$, $p=.01$, $\eta p2=.14$, indicating that the benefit of the sound increased with larger set sizes (i.e., a 639 ms improvement for set size 18, 732 ms for set size 24, 1,423 ms for set size 36, and 3,566 ms for set size 48), but this did not interact with Group $F(3,32)=1.07$, $p=.33$. These results thus indicate that both groups benefitted equally from the presence of sound.

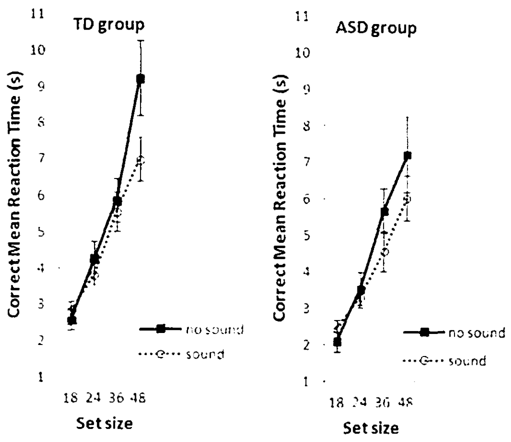


Figure 4. Mean search time (in s) as a function of set size and presence of sound for the adolescents with TD (left panel) and the adolescents with ASD (right panel) group (error bars represent one standard error of mean)

Digital Clock Reading task

Visual latency was calculated for each trial as the difference between the reported and the actual digit in the target stream. Responses up to three digits after the target (corresponding to a visual latency of 600 ms) and one digit before target (corresponding to a 'latency' of -200 ms) were included in the analyses (see Table 3 for the response frequencies). Note that we included responses corresponding to one digit before the cue (so the target location was still unknown) because participants reported on a significant amount of the trials (~18%) the digit that was presented before the cue, presumably because they maintained a visual representation of that display. Five participants were excluded from analyses because they did not complete the task due to a lack of test time (two in the TD group, three in the ASD group). Figure 5 shows the mean latencies for each group and each condition. An overall ANOVA on the visual latencies was conducted with Group (ASD group and TD group) as between-subject factor and Sound (visual only, ~100 ms before the cue or ~200 ms before the cue) as within-subject factor. The ASD group was on average equally fast as the TD group (84 ms for the TD group and 78 ms for the ASD group), $F(1,37)<1$. There was a main effect of Sound, $F(2,36)=5.578$, $p=.006$, $\eta p2=.13$. Post hoc t-tests (Bonferroni corrected) indicated that the average visual latencies of both groups were faster in the ~200 ms SOA condition (65 ms) than the visual-only (86 ms) and ~100 ms SOA condition (92 ms). The Group x Sound interaction was not significant ($F<1$). Both groups thus had similar visual latencies and benefitted from a sound presented ~200 ms before the cue (see Table 4 for an overview of group data per experiment).

Table 3. Response Frequencies of the Clock Reading Task per Condition per Group

	% Responses per number of digits before or after target and error						
Condition	-1	0	1	2	3	Error	Total
No sound	17.0%	22.2%	25.9%	6.7%	3.8%	24.4%	100.0%
~100 ms	14.1%	28.4%	27.5%	4.1%	4.1%	21.8%	100.0%
~200 ms	21.3%	28.8%	23.2%	5.5%	3.9%	17.4%	100.0%

ASD Group

	% Responses per number of digits before or after target and error						
Condition	-1	0	1	2	3	Error	Total
No sound	18.5%	17.8%	28.5%	6.7%	3.5%	24.9%	100.0%
~100 ms	18.2%	17.7%	37.9%	5.3%	3.9%	17.1%	100.0%
~200 ms	18.5%	25.1%	31.4%	4.5%	2.9%	17.6%	100.0%

TD Group

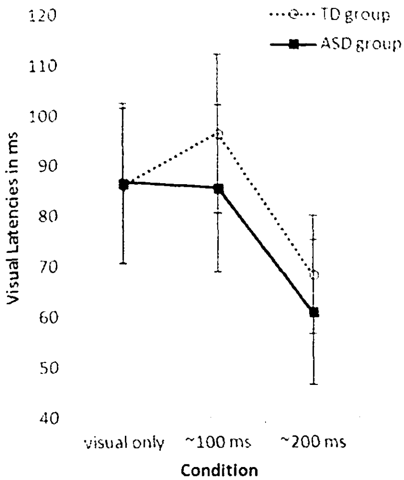


Figure 5. Mean visual latencies (in ms) as a function of presence of sound (error bars represent one standard error of mean)

Table 4. Mean Just Noticeable Difference (JND) and Visual Latencies in ms, Correct Mean Reaction Times in seconds and Standard Deviations per Condition for the ASD Group and the TD Group

	ASD group		TD group	
JNDs per condition in ms				
Visual-only	38.2	(25.0)	25.2	(6.8)
0 ms	26.5	(9.0)	21.4	(4.1)
~100 ms	24.9	(7.8)	20.7	(3.6)
~200 ms	26.1	(10.5)	21.3	(3.1)
~300 ms	24.7	(7.4)	21.5	(4.0)
Reaction times per condition in sec				
No sound / set size 18	2.1	(0.8)	2.6	(1.4)
No sound / set size 24	3.5	(1.3)	4.4	(2.1)
No sound / set size 36	5.7	(3.3)	6.0	(2.9)
No sound / set size 48	7.2	(3.3)	9.5	(4.8)
Sound / set size 18	2.5	(0.8)	2.9	(1.1)
Sound / set size 24	3.3	(1.0)	3.9	(1.3)
Sound / set size 36	4.6	(2.3)	5.7	(2.6)
Sound / set size 48	6.0	(2.4)	7.2	(2.9)
Visual latencies per condition in ms				
Visual-only	86.6	(63.4)	86.0	(72.4)
~100 ms	85.5	(65.9)	96.4	(73.7)
~200 ms	60.9	(57.1)	68.3	(55.2)

Discussion

In the current study we examined visual attention and multisensory integration of low-level audiovisual stimuli (click sounds and flashes) in adolescents with ASD. Adolescents with ASD were, compared with a TD control group, less sensitive to visual TOJs, but had comparable visual search times and visual latencies for orienting attention. Most importantly, in all tasks visual performance of the ASD group improved by the presence of a transient sound at least by equal amounts as in the TD group. There was thus no hint that adolescents with ASD show generalized deficits in MSI of low-level click sounds with visual stimuli.

Our findings from the visual TOJ tasks demonstrate that adolescents with ASD have a reduced sensitivity to visual temporal order. This is in line with a study showing that adolescents with ASD have also reduced sensitivity to audiovisual temporal order (De Boer-Schellekens et al., 2013). These findings also fit a study by Bebko et al. (2006) who found that children with ASD had impairments in the detection of violations of temporal synchrony of audiovisual linguistic stimuli if compared to TD children and children with non-autistic developmental delays. This thus strongly suggest that there are rather specific impairments of (audio)visual temporal sensitivity for synchrony or order in children and/or adolescents with ASD.

Interestingly, the study by Kwakye et al. (2011) who used comparable TOJ tasks, did not find any impairments in the temporal acuity of the visual system. In their study, children with ASD did not differ in the time needed to determine visual order of two circles compared to children with TD. The authors reported that the ASD group required 52.7 ms (the TD group, 60.7 ms) between visual stimuli to determine which circle onset first (with 75% response accuracy). This time appears to be substantially longer than the JNDs in our study (38.2 ms for the ASD group in the visual only condition and 25.2 ms for the TD group). A plausible explanation for this difference could be the participants' age (average 12.2 years for the ASD group in the Kwayke et al. (2011) study compared to 18.8 years in our study) or type of diagnoses (not presented in the Kwakye et al. (2011) study). It remains for future studies to determine whether this difference in age or diagnosis also plays a role in the sensitivity of visual temporal order.

The results from the 'pip-and-pop' visual search task showed no difference in visual search time between the ASD group and the TD group in the silent condition, suggesting that adolescents with ASD, at least in this task, did not have problems with the disengagement, shifting, and engagement of attention. If they had, one would expect them to have longer search times and their slope of the search-time-per-item should be steeper. No evidence for this was found. The ASD group also improved search time, as the TD group did, when a sound was present thus indicating that they had no specific problems with extracting audiovisual synchrony These findings are in contrast with a recent study by Collignon et al. (2012) who also used the 'pip-and-pop' task comparing adolescents with ASD and typical development. These authors reported that the 'pip' did not improve RTs in the ASD group, whereas RTs in the TD group did improve. They also reported that the ASD group was faster compared to the TD group in the tone-absent condition. The authors argued that the absence a 'pip-and-pop' effect in the ASD group is suggestive of atypical MSI, possibly due to long-distance underconnectivity in autism (Brock, Brown, Boucher, & Rippon, 2002; Just, Cherkassky, Keller, & Minshew, 2004). Clearly, though, this suggestion does not fit our findings and it raises the question what causes the difference? One putative explanation might lay in the difference of task instruction. Unlike the Collignon et al. (2012) study, participants in the current study were explicitly told that sounds were synced with a color-change of the target, and that they thus could benefit from the sound. It could be hypothesized that this instruction was used as a top-down strategy in adolescents with ASD to compensate a more bottom-up/ mandatory deficit of MSI. Furthermore, in the study by Collignon et al. (2012) participants were instructed to keep fixation on the dot at the center of the screen, whereas in our study participants were free to use their own search strategy. We chose this approach because there is evidence that people with ASD tend to over-focus on local attributes with a tendency for detail- or feature-based perception (Bertone, Mottron, Jelenic, & Faubert, 2003; Bertone et al., 2005; Kanner, 1943). Frith (1989) also argued that people with autism show detail-focused local processing in which features are perceived and retained at the expense of global configuration and contextualized meaning. Van der Burg et al. (2008), though, reported that at least some distributed visual attention is necessary for observers to notice the synchronized event of the 'pip' and 'pop'. Instructing people with ASD to remain focused on fixation, as in the Collignon et al. (2012) study, may have stimulated the ASD group's local processing strategy at the expense of the more global strategy necessary for intersensory binding. Future studies are necessary to examine this in more detail, but our study suggests that adolescents with ASD are able to use a more global attentional strategy that helps to improve their search time. This also fits recent versions of the 'weak-central-coherence' account in which it has been emphasized that the cognitive style of people with ASD is best considered as a bias towards local processing, rather than a cognitive deficit *per se* (Happé & Booth, 2008). In this view, explicit instructions to focus on the global level may then result in a reduction or obliteration of group differences (Happé & Frith, 2006). Furthermore, our results demonstrate that adolescents with ASD do not have inherent problems with audiovisual integration.

As a final remark on the 'pip-and-pop' visual search task, we would like to shed light on the rather weak effect of sound presence in the TD group when compared to the results of the Van der Burg et al. (2008) study. In their study, facilitative effects of sound presence could already be observed in the set size 24 and 36 condition, while the effects in these set-size conditions in our study seem quite weak. Although this difference is quite puzzling, we would like to suggest a putative explanation. In our experiment sound absence and sound presence conditions were randomized throughout each test block, while in Van der Burg et al. (2008) it was blocked. Possibly, the constant change of search strategy (from serial to parallel and vice versa) might slow-down overall reaction times and diminish the effect of sound, but this remains to be examined in future research.

The results from our spatial orienting task did not show a difference between the ASD and TD group. This suggests that our group of adolescents with ASD did not have problems with the disengagement and shifting of attention. This contrasts with studies that reported evidence for abnormal visual attention in ASD (e.g., Courchesne et al., 1994; Harris et al., 1999; Landry & Bryson, 2004; Wainwright-Sharp & Bryson, 1993). Several other studies, though, found no difference in visual attention (e.g., Senj, Tojo, Dairoku, & Hasegawa, 2004; Van der Geest et al., 2001). Iarocci & Burack (2004) thus demonstrating that the orienting response to peripheral cues in children with ASD was normal. In addition, Leekam, Lopez, & Moore (2000) also failed to find a deficit in shifting attention in children with ASD and actually found that the ASD group was overall faster in orienting to targets. Interestingly, a recent study by Robertson, Kravitz, Freyberg, Baron-Cohen, & Baker (2013) demonstrated that the spatial gradient over which attention enhances visual processing is much sharper in autistic than in matched control participants. The authors suggest that sharper spatial gradients around target locations would predict less interference from distracters and quicker response times in conjunctive visual search, and efficient perception of details in visual scenes. This might also provide an explanation for our findings of intact shifting or disengagement of attention. Although no impairments in shifting or disengagement of attention were reported, the results show that adolescents with ASD benefitted, as the TD group, from the sounds.

A caveat of our study is concerned with the auditory stimuli that we used. In all three tasks, we used short abrupt sounds that are known to have strong alerting properties. Consequently, it is possible that the improvement on visual processing by sound was not driven by MSI as such, but by the alerting properties of the sound. The standard notion to distinguish these accounts is that MSI requires (nearly) simultaneous presentation of audiovisual stimuli, while alerting needs time (~200 ms) to built-up. According to this notion, one might argue that our Experiment 1 (visual TOJ) involved alerting – because the first sound was presented before the first visual stimulus–, Experiment 2 ('pip-and-pop') would be MSI – because the sound was presented together with the target change–, while Experiment 3 would again be alerting – because the sound was always presented before the cue. However, this reasoning is not completely safe because the improvement by sound in the visual TOJ task (temporal ventriloquism) has been demonstrated to depend on the presence of the second sound that is presented after the second visual stimulus (Morein-Zamir, et al., 2003). To complicate matters even more, simultaneous presentation does not guarantee that alerting is not involved because sound processing is generally faster than visual processing. Nevertheless, the 'pip-and-pop' effect cannot be fully explained by increased alertness because the reduction of search time is usually in the order of seconds, as opposed to several milliseconds, and in previous studies, no search benefits were observed when tones preceded the targets by 150 ms (Van der Burg et al., 2008, Experiment 3). In our Experiment 3, though, alerting was likely involved because sounds were presented at the right timing before the cue (~100-200 ms). Most likely, therefore, our results reflect a mix of both intact MSI and intact alerting in ASD, although it is important to notice that alerting on its own cannot account for the whole pattern.

Another caveat is that our results need to be put in a developmental perspective. Sensory difficulties might be present early on during development, but fade away with age, due to several mechanisms. For example, Taylor, Isaac, & Milne (2010) measured audiovisual integration using the 'McGurk effect' in children with ASD and TD children.

They found delayed audiovisual integration, but their results also showed that the ASD group subsequently developed audiovisual integration at a faster rate than the control group. Magnée, De Gelder, Van Engeland, & Kemner (2011) also suggested that it might be possible that sensory difficulties rather than attention problems are primary to MSI abnormalities during childhood. Another factor is the heterogeneity of the ASD group. For example, Rinehart, Bradshaw, Moss, Brereton, & Tonge (2001) reported a deficit specifically in shifting attention in high-functioning autism, but not Asperger's disorder. Here, we examined a very specific group of high-functioning adolescents with ASD and it remains to be examined whether our findings can be generalized to other subtypes. Interpreting the results is also complicated by the heterogeneity of the disorder, even within each subtype. Therefore, our results may not apply to other subpopulations of ASD such as children, adults or lower-functioning people with autism. Additional research will have to consider how visual temporal processing, visual attention, and audiovisual temporal integration varies across subpopulations and how individuals within these groups relate to those with typical development or to those who are both developmentally impaired and non-autistic.

In sum, we have found that adolescents with ASD show diminished sensitivity to visual temporal order without problems in the shifting and/or disengagement of visual attention. Transients sounds substantially improved visual performance, but without sign that this was diminished in ASD. This indicates that adolescents with ASD are unimpaired in the MSI of low-level audiovisual stimuli.

Acknowledgments

We wish to thank all the participating adolescents with ASD for their time and cooperation. We also thank *Yulius Mental Health Institution*, especially the staff of *De Steiger* location *Amazone*. Shan Janki and Sanne de Wildt, thank you for your help on data collection.

References

APA (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington DC: American Psychiatric Association.

Bebko, J. M., Weiss, J. A., Demark, J. L., & Gomez, P. (2006). Discrimination of temporal synchrony in intermodal events by children with autism and children with developmental disabilities without autism. *Journal of Child Psychology and Psychiatry, 47*(1), 88-98.

Berger, H. J. C., Aerts, F., Van Spaendonck, K. P. M., Cools, A. R., & Teunisse, J. P. (2003). Central coherence and cognitive shifting in relation to social improvement in high-functioning young adults with autism. *Journal of Clinical and Experimental Neuropsychology, 25*(4), 502-511. doi: 10.1076/jcen.25.4.502.13870

Bertone, A., Mottron, L., Jelenic, P., & Faubert, J. (2003). Motion perception in autism: a 'complex' issue. *Journal of Cognitive Neuroscience, 15*(2), 218-225. doi: 10.1162/089892903321208150

Bertone, A., Mottron, L., Jelenic, P., & Faubert, J. (2005). Enhanced and diminished visuo-spatial information processing in autism depends on stimulus complexity. *Brain, 128*, 2430-2441.

Brandwein, A. B., Foxe, J. J., Butler, J. S., Russo, N. N., Altschuler, T. S., Gomes, H., & Molholm, S. (2012). The development of multisensory integration in high-functioning autism: High-density electrical mapping and psychophysical measures reveal impairments in the processing of audiovisual inputs. *Cerebral Cortex Advance Access published May 24, 2012.* doi: 10.1093/cercor/bhs109

Brock, J., Brown, C. C., Boucher, J., & Rippon, G. (2002). The temporal binding deficit hypothesis of autism. *Development and Psychopathology, 14*(2), 209-224.

Charbonneau, G., Bertone, F., Lepore, F., Nassim, M., Lassonde, M., Mottron, L., & Collignon, O. (2013). Multisensory deficits in the processing of audiovisual emotion expressions in Autism Spectrum Disorders. *Neuropsychologia.*

Chen, Y. C., & Spence, C. (2011). The crossmodal facilitation of visual object representations by sound: Evidence from the backward masking paradigm. *Journal of Experimental Psychology-Human Perception and Performance, 37*(6), 1784-1802. doi: 10.1037/a0025638

Collignon, O., Charbonneau, G., Peters, F., Nassim, M., Lassonde, M., Lepore, F., . . . Bertone, A. (2012). Reduced multisensory facilitation in persons with autism. *Cortex.* doi: 10.1016/j.cortex.2012.06.001

Courchesne, E., Townsend, J., Akshoomoff, N. A., Saitoh, O., Yeung-Courchesne, R., Lincoln, A. J., . . . Lau, L. (1994). Impairment in shifting attention in autistic and cerebellar patients. *Behavioral Neuroscience, 108*, 848-865.

Crane, L., Goddard, L., & Pring, L. (2009). Sensory processing in adults with autism spectrum disorders. *Autism, 13*(3), 215-228. doi: 10.1177/1362361309103794

De Boer-Schellekens, L., Eussen, M., & Vroomen, J. (2013). Diminished sensitivity to audiovisual temporal order in autism spectrum disorder. *Frontiers in Integrative Neuroscience, 7*(8).

De Gelder, B., Vroomen, J., & Van der Heide, L. (1991). Face recognition and lip-reading in autism. *European Journal of Cognitive Psychology, 3*(69-86).

Foss-Feig, J. H., Kwakye, L. D., Cascio, C. J., Burnette, C. P., Kadivar, H., Stone, W. L., & Wallace, M. T. (2010). An extended multisensory temporal binding window in autism spectrum disorders. *Experimental Brain Research, 203*(2), 381-389. doi: 10.1007/s00221-010-2240-4

Frith, U. (1989). *Autism: Explaining the enigma*. Malden, MA: Blackwell Publishing.

Grossman, R. B., Schneps, M. H., & Tager-Flusberg, H. (2009). Slipped lips: Onset asynchrony detection of auditory-visual language in autism. *Journal of Child Psychology and Psychiatry, 50*(4), 491-497.

Happé, F., & Booth, R. (2008). The power of the positive: Revisiting weak coherence in autism spectrum disorders. *Quarterly Journal of Experimental Psychology, 61*(1), 50-63. doi: 10.1080/17470210701508731

Happé, F., & Frith, U. (2006). The weak coherence account: Detail-focused cognitive style in autism spectrum disorders. *Journal of Autism and Developmental Disorders, 36*(1), 5-25. doi: 10.1007/s10803-005-0039-0

Hari, R., & Renvall, H. (2001). Impaired processing of rapid stimulus sequences in dyslexia. *Trends in Cognitive Sciences, 5*(12), 525-532.

Harris, N. S., Courchesne, E., Townsend, J., Carper, R. A., & Lord, C. (1999). Neuroanatomic contributions to slowed orienting of attention in children with autism. *Cognitive Brain Research, 8*(1), 61-71. doi: 10.1016/s0926-6410(99)00006-3

Iarocci, G., & Burack, J. A. (2004). Intact covert orienting to peripheral cues among children with autism. *Journal of Autism and Developmental Disorders, 34*(3), 257-264. doi: 10.1023/b:jadd.0000029548.84041.69

Just, M. A., Cherkassky, V. L., Keller, T. A., & Minshew, N. J. (2004). Cortical activation and synchronization during sentence comprehension in high-functioning autism: Evidence of underconnectivity. *Brain, 127*, 1811-1821. doi: 10.1093/brain/awh199

Kanner, L. (1943). Autistic disturbances of affective content. *Nervous Child, 2*, 217-250.

Keane, B. P., Rosenthal, O., Chun, N. H., & Shams, L. (2010). Audiovisual integration in high functioning adults with autism. *Research in Autism Spectrum Disorders, 4*(2), 276-289. doi: 10.1016/j.rasd.2009.09.015

Keetels, M., & Vroomen, J. (2011). Sound affects the speed of visual processing. *Journal of Experimental Psychology-Human Perception and Performance, 37*(3), 699-708. doi: 10.1037/a0020564

Kern, J. K., Trivedi, M. H., Grannemann, B. D., Garver, C. R., Johnson, D. G., Andrews, A. A., . . . Schroeder, J. L. (2007). Sensory correlations in autism. *Autism, 11*(2), 123-134. doi: 10.1177/1362361307075702

Kwakye, L. D., Foss-Feig, J. H., Cascio, C. J., Stone, W. L., & Wallace, M. T. (2011). Altered auditory and multisensory temporal processing in autism spectrum disorders. *Frontiers in integrative neuroscience, 4*, 129.

Landry, R., & Bryson, S. E. (2004). Impaired disengagement of attention in young children with autism. *Journal of Child Psychology and Psychiatry, 45*(6), 1115-1122. doi: 10.1111/j.1469-7610.2004.00304.x

Leekam, S. R., Lopez, B., & Moore, C. (2000). Attention and joint attention in preschool children with autism. *Developmental Psychology, 36*(2), 261-273. doi: 10.1037/0012-1649.36.2.261

Magnee, M., De Gelder, B., Van Engeland, H., & Kemner, C. (2011). Multisensory integration and attention in Autism Spectrum Disorder: Evidence from event-related potentials. *Plos One, 6*(8), 5. doi: 10.1371/journal.pone.0024196

Magnée, M. J., De Gelder, B., Van Engeland, H., & Kemner, C. (2008). Audiovisual speech integration in pervasive developmental disorders: Evidence from event-related potentials. *Journal of Child Psychology and Psychiatry, 49*(9), 995-1000.

Magnée, M. J., Oranje, B., Van Engeland, H., Kahn, R. S., & Kemner, C. (2009). Cross-sensory gating in schizophrenia and autism spectrum disorder: EEG evidence for impaired brain connectivity? *Neuropsychologia, 47*(7), 1728-1732. doi: 10.1016/j.neuropsychologia.2009.02.012

Megnin, O., Flitton, A., Jones, C. R. G., De Haan, M., Baldeweg, T., & Charman, T. (2012). Audiovisual speech integration in Autism Spectrum Disorders: ERP evidence for atypicalities in lexical-semantic processing. *Autism Research, 5*(1), 39-48. doi: 10.1002/aur.231

Minshew, N. J., Sweeney, J., & Luna, B. (2002). Autism as a selective disorder of complex information processing and underdevelopment of neocortical systems. *Molecular Psychiatry, 7*, S14-S15. doi: 10.1038/sj.mp.4001166

Mongillo, E. A., Irwin, J. R., Whalen, D. H., Klaiman, C., Carter, A. S., & Schultz, R. T. (2008). Audiovisual processing in children with and without Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders, 38*, 1349-1358.

Morein-Zamir, S., Soto-Faraco, S., & Kingstone, A. (2003). Auditory capture of vision: Examining temporal ventriloquism. *Brain research. Cognitive brain research, 17*(1), 154-163.

Mottron, L., & Burack, J. (2001). Enhanced perceptual functioning in the development of autism. In C. Y. Burack & Zelazo (Eds.), *The development of autism: Perspectives from theory and reserach* (pp. 131-148). Mahwah, NJ: Erlbaum.

Renner, P., Klinger, L. G., & Klinger, M. R. (2006). Exogenous and endogenous attention orienting in Autism Spectrum Disorders. *Child Neuropsychology, 12*(4-5), 361-382. doi: 10.1080/09297040600770753

Rinehart, N. J., Bradshaw, J. L., Moss, S. A., Brereton, A. V., & Tonge, B. J. (2001). A deficit in shifting attention present in high-functioning autism but not Asperger's disorder. *Autism, 5*(1), 67-80. doi: 10.1177/1362361301005001007

Robertson, C. E., Kravitz, D. J., Freyberg, J., Baron-Cohen, S., & Baker, C. I. (2013). Tunnel vision: Sharper gradient of spatial attention in autism. *J Neurosci, 33*(16), 6776-6781. doi: 10.1523/JNEUROSCI.5120-12.2013

Romani, C., Tsouknida, E., Di Betta, A. M., & Olson, A. (2011). Reduced attentional capacity, but normal processing speed and shifting of attention in developmental dyslexia: Evidence from a serial task. *Cortex, 47*(6), 715-733. doi: 10.1016/j.cortex.2010.05.008

Scheier, C. R., Nijhawan, R., & Shimojo, S. (1999). Sound alters visual temporal resolution. *Investigative ophthalmology and visual science, 40*, 4169.

Senju, A., Tojo, Y., Dairoku, H., & Hasegawa, T. (2004). Reflexive orienting in response to eye gaze and an arrow in children with and without autism. *Journal of Child Psychology and Psychiatry, 45*(3), 445-458. doi: 10.1111/j.1469-7610.2004.00236.x

Simmons, D. R., Robertson, A. E., McKay, L. S., Toal, E., McAleer, P., & Pollick, F. E. (2009). Vision in autism spectrum disorders. *Vision Research, 49*(22), 2705-2739. doi: 10.1016/j.visres.2009.08.005

Sireteanu, R., Goebel, C., Goertz, R., Werner, I., Nalewajko, M., & Thiel, A. (2008). Impaired serial visual search in children with developmental dyslexia. In G. F. Eden & D. L. Flower (Eds.), *Learning, skill acquisition, reading, and dyslexia* (Vol. 1145, pp. 199-211). Oxford: Blackwell Publishing.

Smith, E. G., & Bennetto, L. (2007). Audiovisual speech integration and lipreading in autism. *Journal of Child Psychology and Psychiatry, 48*(8), 813-821.

Stekelenburg, J. J., & Vroomen, J. (2005). An event-related potential investigation of the time-course of temporal ventriloquism. *Neuroreport, 16*, 641-644.

Taylor, N., Isaac, C., & Milne, E. (2010). A comparison of the development of audiovisual integration in children with Autism Spectrum Disorders and typically developing children. *Journal of Autism and Developmental Disorders, 40*(11), 1403-1411. doi: 10.1007/s10803-010-1000-4

Teunisse, J. P., Cools, A. R., Van Spaendonck, K. P. M., Aerts, F., & Berger, H. J. C. (2001). Cognitive styles in high-functioning adolescents with autistic disorder. *Journal of Autism and Developmental Disorders, 31*(1), 55-66. doi: 10.1023/a:1005613730126

Van der Burg, E., Olivers, C. N. L., Bronkhorst, A. W., & Theeuwes, J. (2008). Pip and pop: Nonspatial auditory signals improve spatial visual search. *Journal of Experimental Psychology-Human Perception and Performance, 34*(5), 1053-1065. doi: 10.1037/0096-1523.34.5.1053

Van der Geest, J. N., Kemner, C., Camfferman, G., Verbaten, M. N., & Van Engeland, H. (2001). Eye movements, visual attention, and autism: A saccadic reaction time study using the gap and overlap paradigm. *Biological Psychiatry, 50*(8), 614-619. doi: 10.1016/s0006-3223(01)01070-8

Van der Smagt, M. J., Van Engeland, H., & Kemner, C. (2007). Brief report: Can you see what is not there? Low-level auditory-visual integration in Autism Spectrum Disorder. *Journal of Autism and developmental disorders, 37*, 2014-2019.

Vidyasagar, T. R., & Pammer, K. (1999). Impaired visual search in dyslexia relates to the role of the magnocellular pathway in attention. *NeuroReport, 10*, 1283-1287.

Vroomen, J., & De Gelder, B. (2000). Sound enhances visual perception: Cross-modal effects of auditory organization on vision. *Journal of Experimental Psychology-Human Perception and Performance, 26*(5), 1583-1590.

Vroomen, J., & De Gelder, B. (2004). Temporal ventriloquism: Sound modulates the flash-lag effect. *Journal of Experimental Psychology: Human Perception and Performance, 30*(3), 513-518.

Vroomen, J., & Keetels, M. (2006). The spatial constraint in intersensory pairing: No role in temporal ventriloquism. *Journal of experimental psychology: Human perception and performance, 32*, 1063-1071.

Vroomen, J., & Keetels, M. (2009). Sounds change four-dot masking. *Acta Psychologica, 130*(1), 58-63. doi: 10.1016/j.actpsy.2008.10.001

Wainwright, J. A., & Brown, S. E. (1996). Visual-spatial orienting in autism. *Journal of Autism and Developmental Disorders, 26*(4), 423-438. doi: 10.1007/bf02172827

Wainwright-Sharp, J. A., & Bryson, S. E. (1993). Visual orienting deficits in high-functioning people with autism. *Journal of Autism and developmental disorders, 23*, 1-13.

Wallace, M. (2004). The development of multisensory integration. In G. A. Calvert, C. Spence & B. E. Stein (Eds.), *The handbook of multisensory processes* (pp. 625-642). Cambridge MA: MIT.

Chapter 5

Sound can improve visual search in developmental dyslexia

De Boer-Schellekens, L.

Vroomen, J.

Experimental Brain Research 2012; 216(2), 243-248

Abstract

We examined whether developmental dyslexic adults suffer from 'Sluggish Attentional Shifting' (SAS; Hari & Renvall, 2001) by measuring their shifting of attention in a visual search task with dynamic cluttered displays (Van der Burg, Olivers, Bronkhorst, & Theeuwes, 2008). Dyslexics were generally slower than normal readers in searching a horizontal or vertical target among oblique distracters. However, the addition of a click sound presented in synchrony with a color change of the target drastically improved their performance up to the level of the normal readers. These results are in line with the idea that developmental dyslexics have specific problems in disengaging attention from the current fixation, and that the phasic alerting by a sound can compensate for this deficit.

Introduction

Developmental dyslexia is a neurobiological disorder characterized by a difficulty in reading acquisition despite adequate intelligence, conventional education, and motivation (APA, 1994). The prevailing view supports the hypothesis that dyslexia results from a specific deficit of auditory-phonological perception, representation, and phonological memory (see Vellutino, Fletcher, Snowling, & Scanlon, 2004; Ziegler & Goswami, 2005 for reviews). Children and adults with dyslexia show, indeed, deficits in the representation and manipulation of phonological information (e.g., poor speech-sound awareness, slow lexical retrieval and poor phonological short-term memory; see Ramus, 2003, for a review). These deficits could interfere with one of the most critical skills for successful reading acquisition, such as phonological decoding (Share, 1995; Ziegler & Goswami, 2005).

Apart from their phonological difficulties, dyslexic subjects often suffer from a variety of subtle sensory and motor deficits. Whether these deficits have any causal relation to the reading disorder, or are totally independent, is currently under debate. One hypothesis of a visual cause for dyslexia is that the reading disorder is caused by a deficiency in the magnocellular part (also referred to as the 'transient system') of the visual system (Stein & Walsh, 1997). This hypothesis might seem controversial, since one would expect the parvo- rather than the magnocellular pathways to be largely involved with fine pattern vision and object discrimination that are essential for reading. However, studies have indicated a function for the magnocellular dominated dorsal stream in selective attention (Motter, 1993; Vidyasagar, 1998). Vidyasagar and Pammer (1999) suggested that if the magnocellular system (M system) is involved in gating all visual input going through the striate cortex, a deficit in this system would also affect the parvocellular system (P system). This would become manifest in tasks in which there is intense competition for attentional resources and in which the supposed M-mediated attentional spotlight is essential for good performance. Stein (2003) also suggested that a magnocellular deficiency may cause a type of visual attention deficit in dyslexia. This has made it important to assess visual attention in dyslexic readers in more detail. A recent and particularly interesting hypothesis that links the magnocellular deficit with reading problems is that dyslexics may have 'Sluggish Attentional Shifting' (SAS; Hari & Renvall, 2001).

The present study was motivated by the idea that SAS could indeed provide a coherent framework to understand a variety of sensory problems that dyslexics encounter. The basic notion underlying SAS is that sensory input is chunked, and that attention of dyslexic subjects, once engaged on a chunk, cannot be easily disengaged (Hari & Renvall, 2001). This causes impairments in the shift or the focusing of attention (Hari & Renvall, 2001), and it may result in a prolonged attentional dwell time and poor judgments of temporal order (Jáskowski & Rusiak, 2008). SAS can affect fluent reading because the sensory input is prolonged, thereby degrading essential cortical representations (for review, see Hari & Renvall, 2001). In line with this idea, Lallier et al. (2010) used an auditory and visual stream segregation task, and reported that in order to process two successive stimuli separately, dyslexic participants with phonological impairments required a significantly longer inter-stimulus interval than controls regardless of sensory modality. Another important prediction from SAS is that dyslexics may profit from a transient sound because of a general alerting effect that improves the disengagement of attention.

A number of methods have been used to measure visual attention in dyslexics, but so far, none has used sounds to improve search time. In the standard visual search task, participants search for a pre-specified visual target among other distracters. Previous reports are rather consistent with a visual attention deficit in dyslexics, reporting slower search times for dyslexic than normal readers (Casco & Prunetti, 1996; Romani, Tsouknida, Di Betta, & Olson, 2011; Ruddock, 1991; Sireteanu et al., 2008; Vidyasagar & Pammer, 1999; Williams, Brannan, & Latirgue, 1987). In this context, Pammer and Vidyasagar (2005) and Jones et al. (2008) argued that dyslexics may suffer from an impairment in the serial allocation of attention. According to SAS, the slowness of dyslexics can be explained by an impairment in the disengagement of attention from an element in the search set.

Here we thought to add sounds to the visual search task, using the 'pip-and-pop' paradigm by Van der Burg et al. (2008). These authors designed a visual search task in which a target (a horizontal or vertical line) was embedded in a cluttered display of distracters (oblique lines). The targets and distracters changed, on randomly determined times color (and, important from the perspective of the M-system, also luminance) from green-to-red or red-to-green. They found that a simple auditory 'pip' could drastically decrease search times if the 'pip' was synchronized with the color/luminance-change of the target: the 'pip' then made the target 'pop-out'. Further studies have shown that a sound will only lead to benefits in visual search if the changes in the two signals are both synchronized and transient (Van der Burg, Cass, Olivers, Theeuwes, & Alais, 2010). If this condition is met, then the effect will also resist wide spatial misalignment (Fiebelkorn, Foxe, Butler, & Molholm, 2011).

In the current study, we used this paradigm to examine whether a sound would improve the visual search time of dyslexic readers more than it does in normal readers. If, as proposed in SAS, dyslexic readers have problems with the disengagement of attention from the current fixation, one expects them in the tone-absent condition (serial search) to have longer search times than normal readers, and their slope of the search time per item should be steeper (see also Romani et al., 2011; Sireteanu et al., 2008; Vidyasagar & Pammer, 1999). In the sound-present condition, though, the 'pip' can make the target 'pop-out' (parallel search), and search time may become independent of the set size of the distracters. This should be particularly helpful for dyslexic readers, as they may have a specific difficulty with serial, but not parallel search (Sireteanu et al., 2008). Ultimately, then, a single pip may compensate for the dyslexics' visual attention deficit.

Methods

Participants

Fifteen young adults with developmental dyslexia (five males and ten females) and 15 age-matched controls without reading difficulties (five males, ten females) were tested. The dyslexic readers had been diagnosed with developmental dyslexia based on standard exclusion criteria (APA, 1994). They were all formally assessed and diagnosed by clinical and educational psychologists. Their reading achievements (accuracy and/or speed) were additionally assessed via standardized Dutch reading tests for single word and non-word reading (Brus & Voeten, 1997; Van den Bos, Lutje Spelberg, Scheepsma, & De Vries, 1999). Dyslexic participants were selected on the basis of: (1) normal or corrected-to-normal vision and hearing; (2) absence of neurological and/or psychiatric disorders; (3) absence of attention deficit disorder with hyperactivity (because of the high co-morbidity with dyslexia); (4) absence of color-blindness. The controls reported no history of reading problems. The two groups were drawn from the same subject pool of university students, but were significantly different for both accuracy and speed of word and non-word reading (see Table 1 for details). Participants were tested individually, were unaware of the purpose of the experiment, and received course credits or money for their participation. Written consent was obtained from all participants according to the Declaration of Helsinki.

Table 1. Mean and Standard Deviation (SD) of Age (in Years), Word and Non-word Reading Scores (Errors and Speed in Number of Correctly Read Items) in Dyslexics (N=15) and Age-Matched Normal Reading Controls (N=15)

	Dyslexics		Controls		Comparison	
	Mean	SD	Mean	SD	$t(28)$	p
Age	21.5	2.2	20.7	1.7	-1.1	0.28
Word reading						
Errors	1.3	1.1	0.3	0.6	-3.09	**.004***
Speed	77.8	10.3	93.5	16.4	3.16	**.004***
Non-word reading						
Errors	8.9	3.0	2.3	2.9	-6.73	**<0.001***
Speed	69.9	16.2	98.5	14.0	5.17	**<0.001***

*= $p<0.05$

Stimuli

The stimuli were made as in Van der Burg et al. (2008). The auditory stimulus was a short white noise click of 68 ms presented at 74 dB(A) through the laptop speakers. The visual stimuli were presented on a 15-inch, 60 Hz laptop monitor (Dell Inspiron 6000), controlled by E-Prime 1.2 (Psychology Software Tools, Inc.; *http://www.pstnet.com/eprime*). The visual search displays consisted of 24 or 48 red (20 cd/m^{-2}) and green (11 cd/m^{-2}) line segments (length .88° visual angle) against a dark background 0.05 cd/m^{-2}). The initial color (red or green) was randomly determined for each item. The lines were randomly placed in an invisible 10 * 10 grid (10.5° * 6.5°) centered on a white central fixation cross, with the constraint that the target was never presented at the four central positions, to avoid immediate detection. The target was a horizontal or vertical line, while for distracters line orientation deviated randomly by plus or minus 26.5° from horizontal or vertical. The distracters changed color (from red-to-green or vice versa) every 50, 100 or 150 ms. The number of distracters that changed simultaneously during a trial varied for the different set sizes; in set size 24, one, two or four distracters changed simultaneously, while in set size 48 it was one, four or seven distracters. The target changed color every 500 or 1000 ms, and always changed alone. Distracters did not change color from 150 ms before the target until 100 ms after the target had changed color. During the first 500 ms of a trial, the target also did not change color.

Procedure

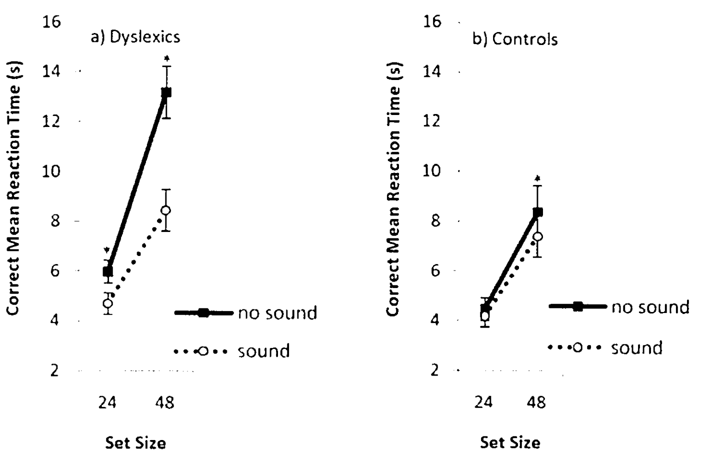
Participants were tested in a dimly lit and sound-proof cabin and were seated approximately 65 cm in front of the laptop screen. Head movements were precluded by a chin-rest. A white fixation cross was illuminated in the center of the screen at the beginning of each trial. Participants were asked to remain focused on the fixation cross. After 150-500 ms the display with target and distracters appeared at the screen. In the sound-present condition, a change in the color of the target was always accompanied by a simultaneously presented sound. The search display was presented until the participants made a response. Participants were instructed to search for the target and to press one of two buttons corresponding with the target orientation '–' or '|' as fast and accurately as possible. All participants were explicitly told that sounds, if present, were synced with a color-change of the target, and that they thus could benefit from the sound because it signaled that the target had changed color. To encourage that participants reacted as fast and as accurately as possibly throughout the whole experiment, written feedback about accuracy and search time was given after each trial. Overall scores were also given at the end of the experiment. A practice session preceded the experimental test that stopped until 10 consecutively correct answers were given.

Design. There were two within-subjects factors: Set size (24 or 48) and Sound (present or absent). These factors were varied randomly across trials. Target orientation was balanced and randomly mixed. The whole test consisted of one block of 80 experimental trials, in which each of the four unique conditions was presented 20 times. The experiment lasted ~15 minutes in total.

Results

The data of the practice session and erroneous responses were excluded from analyses. The overall mean error rate was low (5.8% for the dyslexic group and 4.4% for the control group), and did not significantly differ between groups, $t(28)=1.32$, $p>.05$. No further analyses were therefore performed on error rates. Search time was measured from the onset of the search display until the response to the target. The averaged search times for each condition are presented in Figure 1. An overall repeated measures ANOVA was conducted with Group (dyslexics versus normal readers) as between-subjects factor, and Set size (24 or 48 items) and Sound (sound present or absent) as within-subjects factors. As expected, dyslexics had longer overall search times than normal readers $F(1,28)=5{,}66$, $p<.05$, $\eta p2=.17$ (mean search time of 8,004 ms for dyslexics and 6,100 ms for normal readers). The search time was also faster for the small than large set size $F(1,28)=144.94$, $p<.001$, $\eta p2=.84$ (mean search time of 4,759 ms for set size 24 and 9,351 ms for set size 48), and search time of trials with sound was faster than without sound, $F(1,28)=13.58$, $p<.01$, $\eta p2=.17$ (mean search time of 7,929 ms for sound absent conditions and 6,181 ms for sound present conditions). There was an interaction between Set size and Group, $F(1,28)=7.15$, $p<.05$, $\eta p2=.20$, indicating that dyslexics had slower search times per item than normal readers (dyslexics: 222 ms/item; normal readers: 170 ms/item). Most importantly, there was interaction between Group, Sound, and Set size, $F(1,28)=5.275$, $p<.05$, $\eta p2=.16$. As is clearly visible in Figure 1, and as predicted, both groups benefitted from sound, but the dyslexics profited more from sound than normal readers as their improvement in search times per set size was bigger (an improvement of 1,000 ms for set size 24, and 4,735 ms for set size 48) than that of the controls (an improvement of 281 ms for set size 24, and 976 ms for set size 48).

Separate ANOVAs on the sound-absent and sound-present conditions showed that in the sound-absent conditions, the dyslexics were significantly slower than the normal readers, $F(1,28)=9.15$, $p<.01$, $\eta p2=.25$, and this difference was bigger with the large set size (Set size * Group interaction effect, $F=9.52$, $p<.01$, $\eta p2=.25$). In stark contrast, in the sound-present condition, the search time of the dyslexic group was not different from the control group (main effect of Group, $F<1$, Set size * Group, $F<1$).



* = $p<.05$

Figure 1. Mean search time (in s) as a function of set size and presence of sound for the dyslexic (left panel) and normal reading (right panel) group (error bars represent one standard error of mean)

Discussion

Here we examined the effect of sound on visual search times of dyslexic versus normal readers, using the 'pip-and-pop' task. Our results confirmed, in accordance with predictions from SAS, that (1) in the sound-absent condition, dyslexics' search time was much longer than of normal readers, (2) in the sound-absent condition, dyslexics' search time increased more strongly with an increase in set size than of normal readers, and (3) that dyslexics' search time improved drastically by the presence of a transient sound; in fact their search time then became as good as normal readers.

The general slowness of the dyslexic group is consistent with previous studies using visual search tasks (e.g., Romani et al., 2011; Sireteanu et al., 2008; Vidyasagar & Pammer, 1999). These findings are in accordance with the SAS account of Hari and Renvall (2001), according to which the dyslexics' automatic attention system cannot disengage fast enough from one item to move to the next. This results in a prolonged dwell time and large effect of set size.

The improvement in performance by the presence of the sound leads to the question why a transient sound could speed up the orienting of attention of dyslexic readers as much as it does. First of all, it is important to note that the sound used in the experiment did not bias attention towards a specific direction or location. We used a static sound which was centrally presented, so the sound was not informative about the possible location of the target. The gain offered by the sound for dyslexic readers is in line with other findings demonstrating that dyslexics have specific problems in serial, but not parallel search. For example, Sireteanu et al. (2008) demonstrated that dyslexics, compared to normal readers, have difficulties in serial, but not parallel search. Our results are consistent with this finding (and previous findings by Casco & Prunetti, 1996; Ruddock, 1991; Vidyasagar & Pammer, 1999; Williams et al., 1987) in that we found that in the sound-absent condition, the search time of dyslexic readers increased more with the number of distracters and was significantly slower than that of the normal readers. In the sound-present condition, it has been argued that the binding of synchronized auditory-visual signals occurs rapidly, automatically, and effortlessly, with the auditory signal attaching to the visual signal relatively early in the perceptual process. Through this, a non-spatial auditory event ('pip') can guide attention towards the location of a synchronized visual event that, without an auditory signal, is difficult (Van der Burg et al., 2008). The 'pip' then makes the target 'pop-out', changing a serial search into an automatic, parallel search. This then led to a decrease in dyslexics search times up to the level of normal readers.

Although it is clear that dyslexics were better in parallel search than serial search, one can still ask whether there were – besides SAS – any other reasons why dyslexics benefited significantly more from sound than the normal readers. One clue for this may come from a visual search study by Facoetti et al. (2000). These authors found that dyslexic children had a bigger 'pop-out' effect, which is a characteristic of parallel *processing. The authors argued that dyslexia is characterized by a difficulty to narrow the* attentional focus, and dyslexics therefore tended to adopt a more distributed focus of attention. In addition, Van der Burg et al. (2008) suggested that at least some distributed attention is necessary for observers to notice the synchronized event of the 'pip' and 'pop'. By combining these two notions, it may become understandable why dyslexics, presumably with a more distributed focus of attention, could profit more from sound than normal readers.

Plausible explanations for the substantial benefit of sound by dyslexics might also be derived from studies that examined the effect of sound on visual attention. Robertson et al. (1998) studied patients with neglect and showed that the phasic alerting by a transient non-spatial sound can overcome their spatial deficits in visual awareness. This finding provides evidence that the phasic alerting alone can directly affect the speed of perceptual processing, rather than merely affecting motor readiness. Follow-up studies by Van der Burg et al. (2008, 2011) however, found evidence for a very early multisensory interaction that ruled out that the 'pip-and-pop' effect is due to increases of alertness, as the effect follows a time course that is quite different from alerting effects.

Doyle and Snowden (2001) also examined the effects of simple auditory signals whose onset was synchronized with that of the visual target, but provided no information about the target location. Their findings made them speculate that an auditory signal may promote attentional disengagement (for similar reasoning, see Keetels & Vroomen, 2011). Related to our study, the sound may thus have a facilitatory effect on the disengagement of attention of the dyslexic readers, making them process the visual target (much) sooner when accompanied by a sound relative to when visual information is presented alone.

A final speculation about the reason for the bigger improvement by sound in the dyslexic group may be related to cross-modal temporal deficits that have been found in dyslexia. As demonstrated by Van der Burg et al. (2008), in order to be effective, a sound needs to be presented in close temporal proximity to the visual target change. This thus demands intact cross-modal temporal integration. Various authors, though, argued that dyslexics exhibit deficits in different sensory systems which involve alterations in temporal information processing (e.g., Kinsbourne, Rufo, Gamzu, Palmer, & Berliner, 1991; Laasonen, Service, & Virsu, 2002; Tallal, 1980). One hypothesis confirmed by Hairston et al. (2005) could be relevant. The authors found support for the idea of altered cross-modal temporal processing in dyslexia, as they reported that dyslexic subjects showed an extended temporal window for binding visual and auditory cues. These findings could be potentially relevant for our results, because an enlarged temporal window may lead to a bigger 'pip-and-pop' effect in the dyslexics, as they may profit over an extended period of time of the sound. It should be noted, though, that an enlarged temporal window of integration may also lead to more spurious binding between the sound and color changes of distracters. An enlarged temporal window would then interfere rather than being of help in visual search time. Future studies that vary the SOA between sound and target and the SOA between sound and distracter change might give more detailed information on this and on the mechanisms of multisensory integration in dyslexic readers.

To summarize, our results showed that dyslexic readers have problems with visual *serial search*. This is evidence for visual attentional abnormalities in dyslexia, more specifically in the disengagement and shifting of attention. Most interestingly, though, a spatially non-informative transient sound could overcome these abnormalities. It remains for future studies with other clinical populations who are thought to have difficulties with disengaging and shifting attention (e.g., high-functioning autistic individuals) to further explore the effects of sound on visual attention.

References

APA (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington DC: American Psychiatric Association.

Brus, B. T., & Voeten, M. J. M. (1997). *Een-Minuut-Test*. Amsterdam: Pearson.

Casco, C., & Prunetti, E. (1996). Visual search in good and poor readers: Effects with single and combined features targets. *Perceptual and Motor Skills, 82*, 1155-1167.

Doyle, M. C., & Snowden, R. J. (2001). Identification of visual stimuli is improved by accompanying auditory stimuli: The role of eye movements and sound location. *Perception, 30*(7), 795-810.

Facoetti, A., Paganoni, P., & Lorusso, M. L. (2000). The spatial distribution of visual attention in developmental dyslexia. *Experimental Brain Research, 132*, 531-538.

Fiebelkorn, I. C., Foxe, J. J., Butler, J. S., & Molholm, S. (2011). Auditory facilitation of visual-target detection persists regardless of retinal eccentricity and despite wide audiovisual misalignments. *Experimental Brain Research, 213*(2-3), 167-174. doi: 10.1007/s00221-011-2670-7

Hairston, W. D., Burdette, J. H., Flowers, D. L., Wood, F. B., & Wallace, M. T. (2005). Altered temporal profile of visual-auditory multisensory interactions in dyslexia. *Experimental Brain Research, 166*(3-4), 474-480. doi: 10.1007/s00221-005-2387-6

Hari, R., & Renvall, H. (2001). Impaired processing of rapid stimulus sequences in dyslexia. *Trends in Cognitive Sciences, 5*(12), 525-532.

Jones, M. W., Branigan, H. P., & Kelly, M. L. (2008). Visual deficits in developmental dyslexia: Relationships between non-linguistic visual tasks and their contribution to components of reading. *Dyslexia, 14*(2), 95-115. doi: 10.1002/dys.345

Jáskowski, P., & Rusiak, P. (2008). Temporal order judgment in dyslexia. *Psychological research, 72*, 65-73.

Keetels, M., & Vroomen, J. (2011). Sound affects the speed of visual processing. *Journal of Experimental Psychology-Human Perception and Performance, 37*(3), 699-708. doi: 10.1037/a0020564

Kinsbourne, M., Rufo, D. T., Gamzu, E., Palmer, R. L., & Berliner, A. K. (1991). Neuropsychological deficits in adults with dyslexia. *Developmental Medicine and Child Neurology, 33*(9), 763-775.

Laasonen, M., Service, E., & Virsu, V. (2002). Crossmodal temporal order and processing acuity in developmentally dyslexic young adults. *Brain and Language, 80*(3), 340-354. doi: 10.1006/brln.2001.2593

Lallier, M., Tainturier, M.-J., Dering, B., Donnadieu, S., Valdois, S., & Thierry, G. (2010). Behavioral and ERP evidence for amodal sluggish attentional shifting in developmental dyslexia. *Neuropsychologia, 48*, 4125-4135.

Motter, B. C. (1993). Focal attention produces spatially selective processing in visual cortical areas V1, V2 and V4 in the presence of competing stimuli. *Journal of Neurophysiology, 70*(3), 909-919.

Pammer, K., & Vidyasagar, T. R. (2005). Integration of the visual and auditory networks in dyslexia: A theoretical perspective. *Journal of Research in Reading, 28*(3), 320-331.

Ramus, F. (2003). Developmental dyslexia: specific phonological deficit or general sensorimotor dysfunction? *Current Opinion in Neurobiology, 13*(2), 212-218. doi: 10.1016/s0959-4388(03)00035-7

Robertson, I. H., Mattingley, J. B., Rorden, C., & Driver, J. (1998). Phasic alerting of neglect patients overcomes their spatial deficit in visual awareness. *Nature, 395*(6698), 169-172.

Romani, C., Tsouknida, E., Di Betta, A. M., & Olson, A. (2011). Reduced attentional capacity, but normal processing speed and shifting of attention in developmental dyslexia: Evidence from a serial task. *Cortex, 47*(6), 715-733. doi: 10.1016/j.cortex.2010.05.008

Ruddock, K. H. (1991). Visual search and dyslexia. In J. F. Stein (Ed.), *Vision and visual dyslexia* (Vol. 13, pp. 58-79). London: MacMillan Press.

Share, D. L. (1995). Phonological recoding and self-teaching - Sine-qua-non of reading acquisition. *Cognition, 55*(2), 151-218. doi: 10.1016/0010-0277(94)00645-2

Sireteanu, R., Goebel, C., Goertz, R., Werner, I., Nalewajko, M., & Thiel, A. (2008). Impaired serial visual search in children with developmental dyslexia. In G. F. Eden & D. L. Flower (Eds.), *Learning, skill acquisition, reading, and dyslexia* (Vol. 1145, pp. 199-211). Oxford: Blackwell Publishing.

Stein, J., & Walsh, V. (1997). To see but not to read; The magnocellular theory of dyslexia. *Trends in Neurosciences, 20*(4), 147-152.

Tallal, P. (1980). Auditory temporal perception, phonics and reading disabilities in children. *Brain and Language, 9*(2), 182-198.

Van den Bos, K. P., Lutje Spelberg, H. C., Scheepsma, A. J. M., & De Vries, J. R. (1999). *De Klepel: Pseudowoordentest*. Amsterdam: Harcourt Test Publishers.

Van der Burg, E., Cass, J., Olivers, C. N. L., Theeuwes, J., & Alais, D. (2010). Efficient visual search from synchronized auditory signals requires transient audiovisual events. *Plos One, 5*(5), 11.

Van der Burg, E., Olivers, C. N. L., Bronkhorst, A. W., & Theeuwes, J. (2008). Pip and pop: Nonspatial auditory signals improve spatial visual search. *Journal of Experimental Psychology-Human Perception and Performance, 34*(5), 1053-1065. doi: 10.1037/0096-1523.34.5.1053

Van der Burg, E., Talsma, D., Olivers, C. N. L., Hickey, C., & Theeuwes, J. (2011). Early multisensory interactions affect the competition among multiple visual objects. *Neuroimage, 55*(3), 1208-1218. doi: 10.1016/j.neuroimage.2010.12.068

Vellutino, F. R., Fletcher, J. M., Snowling, M. J., & Scanlon, D. M. (2004). Specific reading disability (dyslexia): What have we learned in the past four decades? *Journal of Child Psychology and Psychiatry, 45*(1), 2-40. doi: 10.1046/j.0021-9630.2003.00305.x

Vidyasagar, T. R. (1998). Gating of neuronal responses in macaque primary visual cortex by an attentional spotlight. *Neuroreport, 9*(9), 1947-1952.

Vidyasagar, T. R., & Pammer, K. (1999). Impaired visual search in dyslexia relates to the role of the magnocellular pathway in attention. *Neuroreport, 10*(6), 1283-1287.

Williams, M. C., Brannan, J. R., & Latirgue, E. K. (1987). Visual search in good and poor readers. *Clinical Visioin Science, 1*, 367-371.

Ziegler, J. C., & Goswami, U. (2005). Reading acquisition, developmental dyslexia, and skilled reading across languages: A psycholinguistic grain size theory. *Psychological Bulletin, 131*(1), 3-29. doi: 10.1037/0033-2909.131.1.3

Chapter 6

Multisensory integration compensates loss of sensitivity of visual temporal order in the elderly

De Boer-Schellekens, L.

Vroomen, J.

Submitted

Abstract

Here, we examined sensitivity of visual, auditory, and audiovisual temporal order in five age groups (20- to 70-years old). We also measured Multisensory Integration (MSI) using a phenomenon known as 'temporal ventriloquism', in which click sounds improve sensitivity of visual temporal order. Results showed that sensitivity of visual, auditory, and audiovisual temporal order declined from 50 years on. However, there was no corresponding decline for MSI as the click sounds actually compensated the loss of sensitivity of visual temporal order in the elderly. Sensitivity of audiovisual temporal order did not correlate with MSI, suggesting that well-preserved explicit judgments about crossmodal temporal order are not required for MSI to occur.

Introduction

In our everyday life, we are constantly exposed to information received through our different senses. Our brain has to properly integrate these information sources into one coherent percept. This process of Multisensory Integration (MSI) is a continuously occurring phenomenon that shapes our view of the world and it is therefore crucial for our social and adaptive behavior (Wallace, 2004). MSI has been well-studied over the last decade. In the last few years, there has been a focus on MSI in clinical disorders in which disturbances in (uni) sensory processing are often reported, like Autism Spectrum Disorder (ASD), schizophrenia, and developmental dyslexia. Some have argued that the integration of multisensory processing must logically follow from integrity and fidelity of processing within the constituent unisensory systems. Thus, should there be sensory-specific deficits, for example in audition or vision, one could reasonably expect that audiovisual integration might also show deficits (Foxe & Molholm, 2009). Deficits in MSI then lead to difficulties in attributing meaning to incoming stimuli that may eventually lead to misinterpretation and miscommunication (core symptoms in ASD and schizophrenia). In the current study, we asked whether this logic applies to the elderly as well. That is, from the elderly it is well-known that there is a general decline in processing speed of the unimodal senses: Does this decline affect MSI as well, or is it the case that MSI can actually compensate this deficit?

To examine this, we started from the consensus that sensitivity for perceiving the correct temporal order of two rapidly presented sequential stimuli like two flashes, two clicks, or a click-flash, declines with age (Corso, 1971; Craig, Rhodes, Busey, Kewley-Port, & Humes, 2010; Habak & Faubert, 2000; Keller, Morton, Thomas, & Potter, 1999; Nusbaum, 1999; e.g., Weiss, 1963). As an example, a study by Busey et al. (2010) found that older individuals performed significantly worse than younger people in a series of visual Temporal Order Judgment (TOJ) tasks that required participants to report the order of sequentially presented letters. Does this slowing in vision imply that MSI is impaired as well, possibly because MSI is rather sensitive to appropriately aligned inputs of the corresponding senses? Interestingly, a number of studies that examined MSI in the elderly have demonstrated that MSI in older adults is actually enhanced (Diaconescu, Hasher, & McIntosh, 2013; Diederich, Colonius, & Schomburg, 2008; Laurienti, Burdette, Maldjian, & Wallace, 2006; Mahoney, Verghese, Dumas, Wang, & Holtzer, 2012; Peiffer, Mozolic, Hugenschmidt, & Laurienti, 2007). For example, Laurienti et al. (2006) examined the speed of discrimination response of aged and young individuals to the presentation of visual, auditory, and combined visual-auditory stimuli. They found that, although the presentation of the audiovisual stimuli speeded response times in both groups, the performance gain was significantly greater in the aged. The authors suggested that despite the decline in sensory processing that accompanies aging, the use of multiple sensory channels may offer an effective compensatory strategy to overcome these unisensory deficits. However, not all studies point in the direction of enhanced MSI in the elderly. For example, a magnetoencephalography (MEG) study by Stephen et al. (2010) reported suppressed cortical MSI response in the elderly, which corresponds with slower reaction times (RTs) and reduced RT facilitation. The authors suggested that this may be related to poor cortical integration based on timing changes in unisensory processing in the elderly.

In aging research, most studies have used tasks that rely on speeded motor acts (e.g., speeded reaction times), thus potentially conflating age-related changes in perceptual and motor components. Tasks that are independent of any requirement to make speeded motor response may possibly provide a purer measure of perceptual processing changes across age (Poliakoff, Shore, Lowe, & Spence, 2006; Shore, Burack, Miller, Joseph, & Enns, 2006). From this view, TOJ tasks are well suitable for examining the ability to accurately perceive the temporal order of uni- or multisensory stimuli. Indeed, a majority of TOJ studies in aging research has found diminished sensitivity of temporal order in older adults compared to younger adults (Busey, Craig, Clark, & Humes, 2010; Setti et al., 2011; e.g., Virsu, Lahti-Nuuttila, & Laasonen, 2003). For example, Poliakoff et al. (2006) used a visuotactile TOJ task to examine the effects of aging on crossmodal temporal perception. They found that older observers required more time to accurately perceive the temporal order of the visuotactile stimuli as compared to younger observers. According to the authors, their results confirmed that aging deleteriously affects crossmodal temporal processing.

In the current study, we used five age groups (between 20-70 years with 10-year-intervals) to trace the development of sensitivity for temporal order in the auditory, visual, and crossmodal (audiovisual) domain using standard visual, auditory, and audiovisual TOJ tasks. In addition, we measured MSI using a phenomenon known as 'temporal ventriloquism'. Here, the basic finding is that an abrupt click sound can attract the appearance of when a flash occurs in time. A sound before a flash (at 100 ms) can make a flash appear earlier, and a sound after the flash (also at 100 ms) can make the flash appear later if compared to a synchronous sound or a silent condition (Morein-Zamir, Soto-Faraco, & Kingstone, 2003; Scheier, Nijhawan, & Shimojo, 1999; Stekelenburg & Vroomen, 2005; Vroomen & De Gelder, 2004; Vroomen & Keetels, 2006). One way to demonstrate this is by means of a visual TOJ task in which participants judge which of two flashes appeared first. When two click sounds are 'sandwiched', one before the first flash and one after the second flash, sensitivity to visual temporal order improves because the apparent Stimulus Onset Asynchrony (SOA) between the two flashes is increased (see Figure 1A). This improvement of sensitivity for visual temporal order is our key measure of MSI and is referred to as the temporal ventriloquist effect (TVE). The question here is whether TVE varies with age. If MSI hinges on well-preserved unimodal and/or crossmodal temporal order in the brain, then older people may have a diminished TVE because sounds may then not get well-integrated with flashes. Alternatively, if MSI does not hinge on a well-preserved percept of unimodal and crossmodal temporal order, then the TVE in the elderly might actually be greater than in the younger because sounds can now compensate the visual deficit in the elderly. Note that the choice of our tasks also allowed us to address whether sensitivity in the audiovisual TOJ task, signaling explicit knowledge of audiovisual temporal order, goes hand-in-hand with MSI. To the extent that MSI indeed requires well-preserved explicit knowledge about crossmodal temporal order, one might expect sensitivity in the audiovisual TOJ task to correlate with the TVE: good sensitivity in the audiovisual TOJ task then should lead to a large TVE effect.

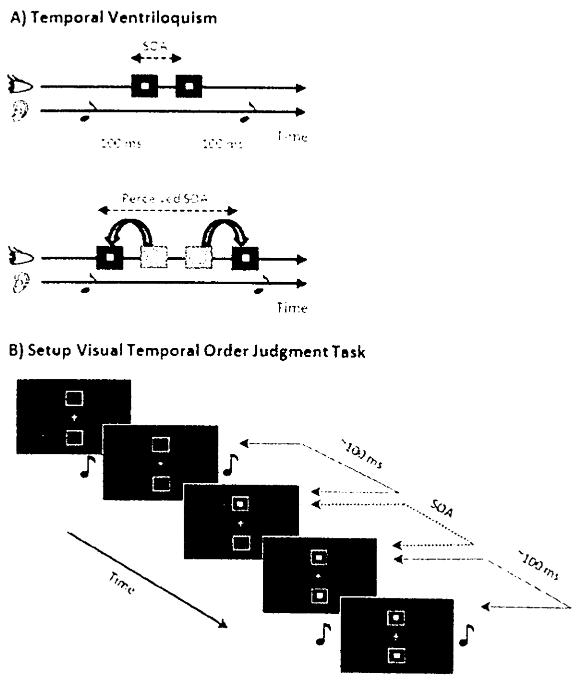


Figure 1. (A) Upper panel: Two lights are flashed with a variable SOA while a sound is presented before the first light and after the second light. Lower panel: The sounds increase the perceived SOA between the two lights, presumably because they attract the apparent onset of the lights. Perceivers then become more sensitive to judge temporal order. (B) A depiction of a trial in the visual TOJ task in the ~100 ms audiovisual delay condition

Methods

Participants

Fifty adults participated, divided over five age categories; 20-29 years (N=10, M=22.1, SD=3.2), 30-39 years (N=9, M=33, SD=2.1), 40-49 years (N=10, M=44.1, SD=2.6), 50-59 years (N=10, M=52.5, SD=1.8) and 60-69 years (N=11, M=65.4, SD=3.6). The 20-29-year-olds were students from Tilburg University. All other participants were recruited through social networks. All subjects were sampled from a healthy, non-psychiatric, population without self-reported complaints of serious medical, neurological or psychiatric illness, seizure disorder, trauma, or use of medication affecting the nervous system. All participants reported normal hearing and normal or corrected to normal seeing. Each participant was tested individually and was naive to the purpose of the study. They gave informed consent to participate in the study according to the Declaration of Helsinki.

Stimuli and design

The visual stimuli were presented on a 15-inch, 60 Hz laptop monitor (Dell Inspiron 6000), controlled by E-Prime 1.2 (Psychology Software Tools, Inc.; *http://www.pstnet.com/eprime*). Auditory stimuli were presented through a headphone (Philips SBC 487). Participants were seated approximately 60 cm in front of the laptop screen. Responses were recorded via a Serial Response Box.

Visual TOJ task (with or without additional clicks)

Stimuli and procedure were similar to previous studies (e.g., Vroomen & Keetels, 2006) and were optimized to examine a temporal ventriloquist effect over an extended range of sound-light intervals. Two white (100 cd/m^{-2}) squares (diameter of 1.5 cm) were presented against a dark (0.05 cd/m^{-2}) background at variable SOAs in two gray placeholders (diameter of 3.5 cm). The squares were presented at 2.4 degrees above and below a central fixation cross (see Figure 1B). The accessory auditory stimuli consisted of two short white noise clicks of 2 ms at 71 dB(A) presented through a headphone. A small red cross served as a fixation point and was placed at eye-level, at central location. There were two within-subject factors: The Audiovisual Interval (3 levels) between the onsets of the first-sound and first-light and the second-light and second-sound (intervals at either ~0 ms or ~100 ms), plus a visual-only condition that served as a baseline for measuring the TVE and as a pure measure of visual temporal order. The other factor was the SOA between the upper and lower square (12 levels: ±533 ms, ±267 ms, ±133 ms, ±67 ms, ±33 ms and ±16 ms, with negative values indicating that the lower visual stimulus was presented first). This resulted in 36 unique trials, each presented 16 times in total in four blocks of 144 trials each. Within blocks, all combinations of SOA and audiovisual interval varied randomly.

A trial consisted of the onset of the first visual stimulus and, after a variable SOA, the second visual stimulus was presented. The two squares remained on the screen until a response was made. Sounds (if present) were presented at the various audiovisual lags, depending on condition. Participants were instructed not to pay attention to the sounds as they did not predict in any sense which stimulus appeared first. Participants judged whether the upper or the lower square had appeared first by pressing a corresponding key on the response box. The next trial started ~800 ms after a response was given.

Auditory TOJ task

The auditory stimuli consisted of two 20 ms 1000 Hz tones which were presented as click tones at either the right or left ear at 75 dB through a headphone. The first tone was presented either in the left ear or right ear and the second tone on the opposite side. A small red cross served as a fixation point and was placed at eye-level, at central location. The SOAs between the first and second tone varied in ten levels; ±600 ms, ±300 ms, ±150 ms, ±75 ms and ±38 ms, with negative values indicating that the tone was presented to the left ear first. Each trial was presented 16 times in total, in two blocks of 80 trials each with SOA varying randomly. Participants judged whether the tone appeared first in the left ear or right ear by pressing a corresponding key on a response box. The next trial started ~1000 ms after a response was given.

Audiovisual TOJ task

The visual stimulus consisted of a square light (diameter of 1.5 cm) surrounded by a placeholder with a diameter of 3.5 cm presented in the center of the laptop screen. The auditory stimulus was a 7 ms stereo sound burst at 75 dB from central location presented through a headphone. Either the light or the sound was presented first and after a variable SOA, the other stimulus was presented. The SOAs between the stimuli varied in ten levels; ±800 ms, ±400 ms, ±200 ms, ±100 ms and ±50 ms, with negative values indicating that the light was presented first. Each trial was presented 16 times in total, in two blocks of 80 trials each. Within blocks, the SOAs were varied randomly. Participants judged whether the auditory or the visual stimulus was presented first by pressing a corresponding key on a response box. The next trial started ~1000-1500 ms after a response was given.

Before each test, a verbal instruction and a practice session were given. Instructions specified that responses were always unspeeded with an emphasis on accuracy. During practice, trials were presented at the two longest SOAs for each condition while participants received feedback ('Wrong' or 'Correct') after each trial. Practice continued until six consecutive correct answers were given. Testing then started without feedback. There was a short pause after each block.

Results

Visual, Auditory, and Audiovisual TOJ tasks

To obtain a measure of sensitivity of temporal order, data were analyzed as in previous studies by fitting a logistic function on the raw data (e.g., Vroomen & Keetels, 2006)[1]. The overall data of one 50-year-old was excluded from further analyses because of diverted behavior during testing which may have influenced results. Furthermore, the audiovisual TOJ data of one of the 40-year-olds and auditory TOJ data of one of the 60-year-olds were excluded from further analyses, because their results did not conform to a typical s-shaped function (respectively, R^2=.42 and R^2=.62 for the 40-year-old participant and the 60-year-old participant). Trials of the practice session and trials with the largest SOAs (for the visual TOJ; ±533 and ±267 ms, for the audio TOJ; ±600 and ±300 ms and for the audiovisual TOJ; ±800 ms) were excluded from further analyses because most participants performed nearly perfectly at these intervals, and therefore no additional variance was

[1] For each group JNDs were fitted by the linear function. The mean and standard deviations of R^2 for the 20-year-olds were .84(±.06), .78(±.12), .81(±.12), .88(±.08) and .88(±.06) for the visual, (three conditions; visual-only, 0, 100 ms), auditory and audiovisual TOJ task, .88(±.07), .82(±.09), .86(±.04), .87(±.10) and .91(±.05) for the 30-year-olds, .84(±.09), .82(±.08), .86(±.07), .88(±.08) and .87(±.06) for the 40-year-olds, .88(±.09), .90(±.06), .87(±.07), .90(±.06) and .79(±.14) for the 50-year-olds and .86(±.11), .84(±.11), .89(±.04), .88(±.06) and .86(±.08) for the 60-year-olds.

accounted for by these measurements (see also Keetels & Vroomen, 2005; Zampini, Shore, & Spence, 2003). The individual proportion of 'upper light first' (visual TOJ), 'left first' (audio TOJ) and 'sound first' (audiovisual TOJ) responses for each combination of stimulus condition and SOA were converted into equivalent Z-scores, and for each condition, the best fitting straight line was then calculated over the SOAs. The lines' slopes were used to determine the just noticeable difference (JND=.675/slope). The JND represents the smallest interval between two stimuli needed by participants to correctly judge which stimulus came first on 75% of the trials. A small JND thus reflects sensitivity being good, as smaller stimulus differences are required to correctly judge temporal order (see Table 1 for individual demographics and JNDs per TOJ task per participant).

The JNDs for each group and task are presented in Figure 2 (upper panel). As is clearly visible, across all tasks, sensitivity declined with age as the elderly were less sensitive (larger JNDs) than the younger participants (see also Table 2). JNDs were smallest in the visual task, somewhat bigger in the auditory task, and relatively large in the audiovisual task. These generalizations were confirmed in a 5 (Age group) x 3 (Modality; visual, auditory, or audiovisual) ANOVA on the JNDs. There was a main effect of Age, $F(4,43)=2.86$, $p<.05$, $\eta p2=.21$, indicating that the older participants were overall less sensitive to temporal order than the younger ones. Pair-wise comparisons showed that the JNDs of the 60-year-olds significantly differed from all other age groups, all p's<.05, except for the 50-year-olds ($p=.45$). There was also a main effect of Modality, $F(2,45)=169.64$, $p<.001$, $\eta p2=.80$, because participants across all age groups were most sensitive for visual temporal order, followed by auditory temporal order, followed by audiovisual temporal order (all pair-wise comparisons were significant, p's<.05). The interaction between Age x Modality of the task was not significant, $F(8,39)=1.31$, $p>.05$.

For completeness, similar analyses were run on the point at which the two stimuli (either the two light, clicks or light/sound) were perceived to be subjectively simultaneous (the point of subjective simultaneity, PSS). A 5 (Age group) x3 (Modality) overall ANOVA on the PSSs showed that there was no main effect of Age $F(4,43)=1.94$, $p>.05$, and no interaction between age and modality of the task, $F(8,39)=1.89$, $p>.05$, thus indicating that the point at which stimuli were perceived to be maximally synchronous did not differ between age groups.

Table 1. Individual Demographics and Just Noticeable Difference (JND) in ms per Participant

Subject	Age	Gender	JND visual	JND ~0 ms	JND ~100 ms	JND auditory	JND audiovisual
X20	20	F	24.73	24.24	23.09	27.29	140.11
X21	25	M	26.69	24.75	23.57	26.44	68.65
X22	21	F	23.23	29.68	23.8	42.82	83.48
X23	25	F	39.25	29.28	32.93	57.34	127.42
X24	19	F	30.95	24.81	24.26	28.93	85.06
X25	21	M	22.86	22.05	22.1	24.71	78.66
X26	21	F	28.62	28.29	27.28	57.52	92.75
X27	20	F	35.63	26.39	30.46	47.71	113.42
X28	29	F	24.0	23.33	26.25	25.48	70.39
X29	20	F	32.64	27.73	23.02	48.7	136.95
X30	35	F	24.59	23.16	22.76	64.43	93.01
X31	36	F	24.72	23.96	25.01	30.64	80.61
X32	30	F	29.25	24.19	25.74	29.78	118.54
X33	30	F	24.72	23.96	25.01	30.64	80.61
X34	31	F	23.77	21.66	22.64	34.55	76.13
X35	34	M	26.04	24.64	23.34	46.8	124.79
X36	33	F	24.00	24.11	22.81	31.22	92.5
X37	33	F	20.97	23.38	22.66	40.32	71.17
X38	35	M	24.11	27.6	22.78	29.46	213.6
X40	42	F	34.7	27.45	24.39	60.28	97.29
X41	45	F	24.59	33.49	24.52	27.62	87.86
X42	44	F	25.18	24.77	26.57	30.79	82.99
X43	41	M	29.74	27.97	23.56	26.98	83.37
X44	47	M	23.11	23.58	23.23	27.29	80.12
X45	40	F	25.78	23.53	23.18	33.36	107.54
X46	47	M	39.2	27.24	26.56	46.13	109.23
X47	46	F	31.61	36.43	26.71	114.72	-
X48	46	M	26.67	27.06	26.79	43.39	94.22
X49	45	F	26.12	25.32	23.37	51.69	104.23
X50	54	M	28.92	23.86	22.62	37.07	66.62
X51	51	F	30.78	27.27	22.19	30.78	153.82
X52	53	F	44.48	41.54	28.01	49.14	265.14
X53	50	F	40.40	32.79	33.22	39.28	146.1
X55	56	M	35.26	30.41	27.16	29.16	81.38
X56	53	F	41.3	26.49	24.94	37.36	87.06
X57	53	M	26.72	28.73	26.05	31.81	110.57
X58	51	F	39.36	41.21	32.13	82.02	155.93
X59	52	M	26.72	26.5	24.49	36.18	114.7
X60	60	F	33.46	28.78	25.57	47.7	96.32
X61	62	F	39.63	44.59	30.65	64.4	106.94
X62	67	M	42.09	31.71	27.27	54.88	130.56
X63	68	M	35.59	44.56	25.66	30.19	117.34
X64	68	F	30.84	66.95	35.42	37.2	119.47
X65	68	F	84.60	42.25	34.79	55.77	247.33
X66	64	M	42.38	27.42	27.37	51.55	191.09
X67	68	F	30.93	31.73	26.9	51.13	156.25
X68	60	M	30.91	25.63	22.86	27.15	94.79
X69	66	F	94.34	50.23	46.08	-	217.72
X70	69	M	73.81	46.46	28.86	34.03	100.73

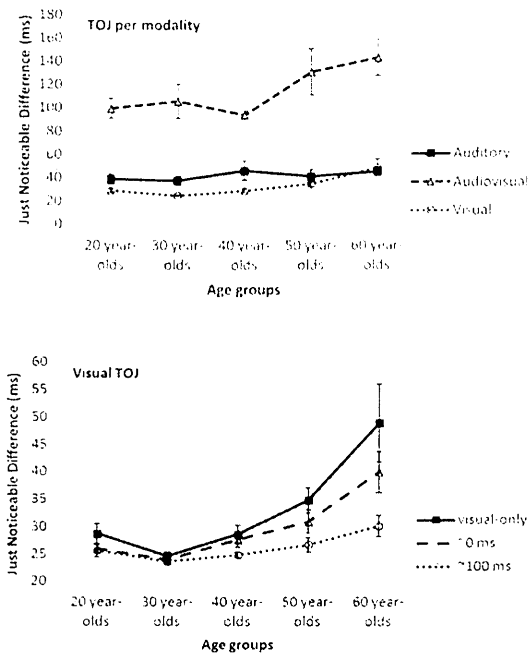


Figure 2. Upper panel: group-averaged JNDs of the visual, auditory and audiovisual TOJ tasks (error bars represent one standard error of the mean). Lower panel: group-averaged JNDs of the visual TOJ task (with or without clicks) as a function of age

Table 2. Mean Just Noticeable Difference (JND) and Standard Deviation (in ms) for each Age Group and Temporal Order Judgment Task

	Temporal Order Judgment Task		
Age group (in years)	Visual	Auditory	Audiovisual
20	28.8 (5.6)	38.8 (13.4)	99.7 (27.4)
30	24.7 (2.2)	37.5 (11.7)	105.7 (44.5)
40	28.7 (5.1)	38.6 (12.2)	94.1 (11.2)
50	34.9 (6.8)	41.4 (16.3)	131.2 (59.7)
60	49.0 (23.5)	45.4 (12.4)	136.1 (15.6)

Temporal Ventriloquist Effect

To obtain a measure of MSI, we computed the improvement in sensitivity of visual temporal order by click sounds presented at ~100 ms sound-light intervals and at ~0 ms versus the silent visual-only condition. The group-averaged proportions of 'upper light first' responses of each group are plotted in Figure 3, and the corresponding JNDs are presented in Figure 2 (lower panel). As is clearly visible, in the visual TOJ task, the two oldest age groups (50- and 60-year-olds) were less sensitive for visual temporal order than the younger-aged groups. As expected, the presence of two click sounds improved visual sensitivity for temporal order across all age groups, and – most importantly – this improvement was actually greatest in the two oldest age groups. This was confirmed in a 5 (Age group) x 3 (Condition: Visual-only, Audiovisual with ~0 ms sound-light intervals, Audiovisual with ~100 ms sound-light interval) ANOVA on the JNDs. There was a main effect of Age group, $F(4,45)=9.53$, $p<.001$, $\eta p2=.46$, indicating that, on average, people in the older age groups had larger JNDs than the younger ones. There was also a main effect of Condition $F(2,47=13.3$, $p<.001$, $\eta p2=.23$, because sensitivity improved for all Age Groups (i.e., lower JNDs) when sounds were present rather than absent (the TVE). The interaction between Age Group x Condition was significant, $F(8,41)=3.01$, $p=.016$, $\eta p2=.22$. As shown in Figure 2 (lower panel) the improvement in JNDs was largest in the two oldest age groups (50- and 60-year-olds) indicating that the elderly profited most from sound.

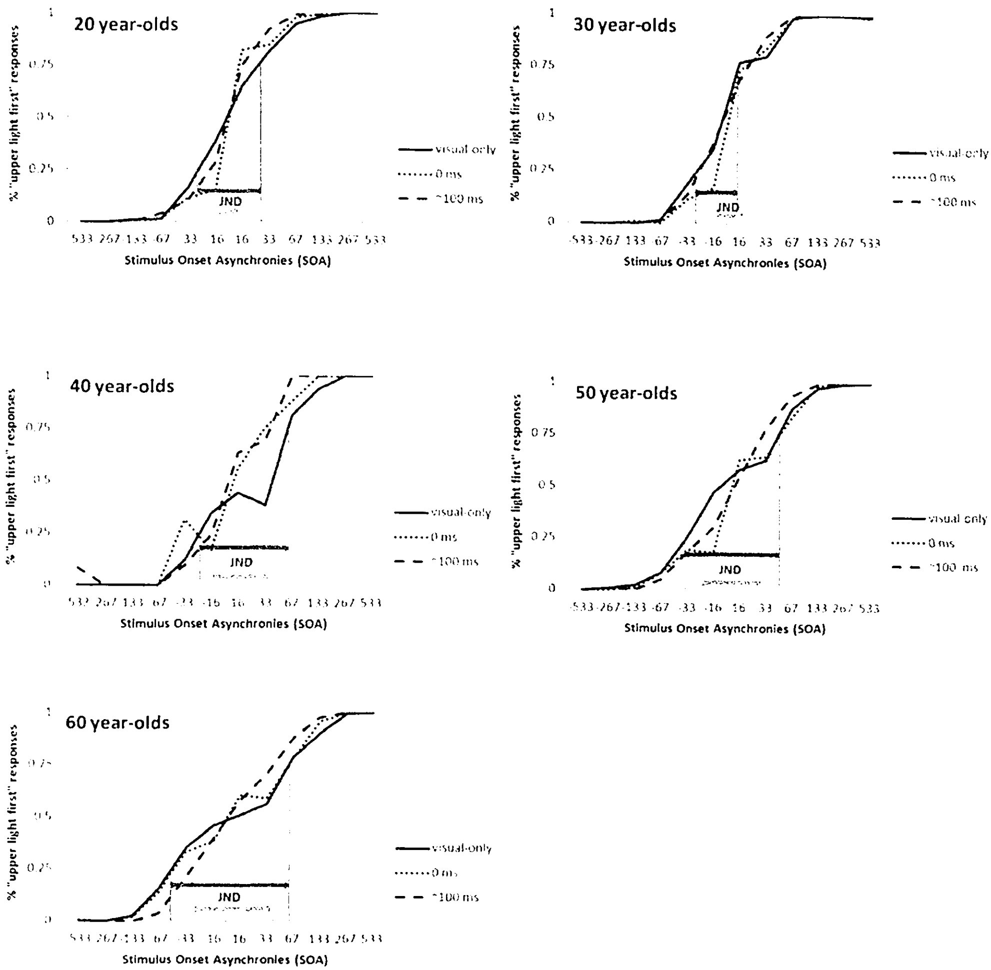


Figure 3. Group averaged proportions of 'upper light first' responses in the visual TOJ task (with and without clicks) and a visualization of the JND

To examine this in more detail, we calculated the TVE as in previous studies by subtracting the JND of the Audiovisual-condition with a sound-light interval of ~100 ms from the Audiovisual-condition with a ~0 ms sound-light interval. This TVE is a relative 'pure' measure of the improvement of sensitivity for visual temporal order by sounds presented at different relative timings (similar results were obtained when the TVE was computed as the improvement by sounds at ~100 ms sound-light interval versus the silent condition). Analyses on the TVE showed that the 20- and 30-year-olds had a significantly smaller TVE than the 50- and 60-year-olds, $t(17)=-2.12$, $p<.05$, $t(19)=-3.0$, $p<.05$, $t(16)=-2.34$, $p<.05$ and $t(18)=-2.90$, $p<.05$ (20-year-olds compared to 50- and 60-year-olds, 30-year-olds compared to 50- and 60-year-olds, respectively). The TVE of the 40-year-olds was also smaller than that of the 60-year-olds, $t(19)=-2.20$, $p<.05$, thus indicating that MSI was enhanced rather than diminished in the elderly.

To further strengthen this, we examined whether the larger TVE in the elderly was caused by a ceiling effect in the younger participants where performance was already very good with little room for improvement. To do so, we calculated a relative improvement by the sound-light interval of ~100 ms relative to the audiovisual condition with sound-light interval of ~0 ms (see Table 3). Analyses on this relative improvement by sound again showed significant differences between the 20- and 30-year-olds and the 50- and 60-year-olds, $t(17)=-2.17$, $p<.05$, $t(19)=-3.0$, $p<.05$, $t(16)=-2.53$, $p<.05$ and $t(18)=-3.52$, $p<.05$ (20-year-olds compared to 50- and 60-year-olds, 30-year-olds compared to 50- and 60-year-olds, respectively). The relative TVE of 40-year-olds was also smaller than that of the 60-year-olds, $t(19)=-2.15$, $p<.05$, thus indicating that the relative TVE was also significantly larger in the elderly.

Table 3. Mean Just Noticeable Difference (JND) and Standard Deviation (in ms) for Each Age Group of the Visual TOJ Task and the Improvement in JND (~0 ms vs ~100 ms) by Sound (in ms and %, TVE)

	JND of Temporal Order Judgment Task			Improvement in JND by sound	
Age group (in years)	Visual only	~0 ms	~100 ms	TVE (in ms)	% TVE
20	28.8 (5.6)	26.1 (2.6)	25.7 (3.6)	0.4	1.2%
30	24.7 (2.2)	24.1 (1.6)	23.6 (1.2)	0.5	1.5%
40	28.7 (5.1)	27.7 (4.2)	24.9 (1.6)	2.8	8.7%
50	34.9 (6.8)	31.0 (6.4)	26.8 (3.9)	4.2	12.3%
60	49.0 (23.5)	40.1 (12.4)	30.1 (6.5)	9.9	21.4%

To assess whether sensitivity for audiovisual temporal order was associated with MSI, we computed the zero-order correlation (Pearson r) between the JNDs of the TOJ tasks and the TVE. If computed across groups, then JNDs of all TOJ tasks correlated strongly with each other and with the TVE (see Table 4), except that the TVE and the JND of the auditory TOJ did not reach significance. The critical correlation between the TVE and the audiovisual JND was positive, $r(48)=.266$, $p<.05$, thus contradicting the idea that good sensitivity in the audiovisual TOJ task (small JNDs) enhance MSI. Rather, it appeared that participants performing most poorly on the TOJ tasks had the largest benefits from sound. However, when the same correlations were computed separately within each age group, correlations differed widely. However, when the same correlations were computed separately within each age group, correlations differed widely.

Table 4. Correlations between the Different Conditions of the TOJ Tasks and Temporal Ventriloquism Effect (TVE)

	JND Visual-only	JND ~0 ms	JND ~100 ms	JND Auditory	JND Audiovisual	TVE
JND Visual-only	____					
JND ~0 ms	.593**	____				
JND ~100 ms	.769**	.725**	____			
JND Auditory	.256*	.280*	.370**	____		
JND Audiovisual	589**	.447**	.505**	.349**	____	
TVE	.286*	.879**	.309*	.170	.266**	____

** $p<0.01$ level
* $p<0.05$ level

Discussion

In this study we examined the effect of age on sensitivity for temporal order and MSI. The results demonstrate three main points: (1) aging has a deleterious impact on sensitivity for auditory, visual, and audiovisual temporal order that becomes noticeable around 50 years; (2) MSI is not diminished in the elderly, but rather can serve as a compensatory mechanism that diminishes the adverse effects of age; (3) sensitivity for audiovisual temporal order does not appear to be good predictor of MSI.

To the best of our knowledge, we were the first to examine the effect of temporal ventriloquism as a measure for MSI in elderly people. As our results showed, all age groups benefitted from the presence of two click sounds (TVE), but the multisensory enhancement was larger in the older groups. These findings of unimpaired or even enhanced MSI in older people are in line with other studies on MSI in the elderly (e.g., Diaconescu et al., 2013; Diederich et al., 2008; Laurienti et al., 2006; Mahoney et al., 2012; Peiffer et al., 2007). Although there is growing evidence for enhanced MSI in the elderly, the question why older adults do exhibit greater integration of multisensory stimuli than younger adults, is still unanswered. Potential sources of enhanced integration in older adults may include inverse effectiveness associated with sensory deficits, alterations in parameters of integration and inefficient top-down modulation of sensory processing (Mozolic, Hayasaka, & Laurienti, 2010). Our results suggest that the use of multiple sensory channels may represent an effective compensatory strategy to overcome unisensory deficits. This is in line with suggestions made by Laurienti et al. (2006) on the speed of discrimination responses of aged and young individuals. These authors reported that the aged showed slower responses to unisensory stimuli, but their gain with multisensory stimuli was significantly greater than in the younger individuals. They furthered that such enhanced multisensory gain is likely the result of compensatory mechanisms which aid in successful multisensory information processing across auditory and visual systems. A similar conclusion was reached by Diaconescu et al. (2013) who examined the spatiotemporal dynamics underlying multisensory responses and age differences in sensory dominance with magnetoencephalography (MEG) recordings during the presentation of complex sounds and semantically-related black-and-white line drawings of animate and inanimate objects. They found that both MSI and visual dominance are more pronounced with age and suggested that enhanced multisensory responses in posterior parietal and medial prefrontal regions may serve a compensatory function as they predict cross-modal facilitation in older adults. Such compensatory effects may arise as a result of gray matter volume changes and reductions in temporal processing during auditory perception that accompanies healthy aging.

According to the principle of inverse effectiveness, older-aged persons may profit more from sound than younger ones because their visual sensitivity is less reliable (larger JNDs), so there is more room for improvement. However, even if we corrected for this by computing a relative improvement, then the effect still remained. A study by Peiffer et al. (2007) on RTs found comparable results, as RTs on unisensory trials were similar for younger and older adults, yet the older adults showed larger multisensory gains than the younger group. This suggests that other mechanisms beyond inverse effectiveness may be required to explain the age-related gains. One hint may come from studies that have demonstrated that multisensory enhancements in the elderly occur over a wider distribution of RTs (Diederich et al., 2008; Laurienti et al., 2006; Peiffer et al., 2007). For example, Laurienti et al. (2006) reported that whereas younger adults showed multisensory behavior facilitation 340-550 ms after stimulus onset, the older adults continued to show enhancements up to 740 ms after the audiovisual stimuli were presented, possibly because elderly have a larger temporal window of integration.

Such enlarged temporal window of integration is also reported by a recent study by Kwakye et al. (2011) in children with ASD. The authors used TOJ tasks with visual, auditory, and audiovisual stimuli and reported no differences in sensitivity for visual temporal order, but thresholds were higher in ASD on the auditory TOJ task. In the multisensory TOJ task, the authors also relied on the TVE and found that children with ASD showed performance improvements over a wider range of temporal intervals than children with typical development. This suggests that children with ASD may also have a wider temporal window of MSI, though more detailed insights into the underlying brain structures is certainly required.

Finally, we would like to shed a light on the developmental perspective of MSI. Our results showed that the deterioration of unisensory temporal sensitivity occurs around the age of 50 years. This raises questions about developmental issues in MSI and whether this age range is possibly accompanied by developmental brain changes. Interestingly, recent work shows that multisensory processing continues to develop into adolescence (Barutchu, Crewther, & Crewther, 2009), suggesting that multisensory processing has a more protracted developmental trajectory than the unisensory systems. In addition, as we age, there are significant changes in all sensory systems and a variety of cognitive functions, like increased hearing thresholds and declines in motor speed, executive function and memory (Birren & Fisher, 1995; Rhodes, 2004). There are also widespread changes in the aging brain, for example, alterations in neurotransmitter systems (Bäckman, Nyberg, Lindenberger, Li, & Farde, 2006) and altered patterns of functional activity during cognitive tasks (Cabeza et al., 2004; Grady, 2008). On the other hand, there is also convincing evidence for developmental issues in MSI in human infants and children (Gori, Del Viva, Sandini, & Burr, 2008; Massaro, 1984; e.g., McGurk & MacDonald, 1976; Nardini, Jones, Bedford, & Braddick, 2008). A recent study by Hillock-Dunn and Wallace (2012) reported changes in audiovisual temporal processing from early childhood through early adulthood and provides evidence that differences in the perception of multisensory temporal relations persist well into adolescence. In line with these developmental perspectives on MSI and the extent of age-related alterations in perception, sensation and cognition, as well as in the anatomy and physiology of the brain, it is not surprising that MSI also changes with age (Mozolic, Hugenschmidt, Peiffer, & Laurienti, 2012).

To conclude, we found older adults to be less sensitive to the temporal order of visual, auditory, and audiovisual stimuli compared to younger adults. However, elderly persons showed enhanced MSI to low-level audiovisual stimuli. MSI in the elderly is an interesting societal topic given the proportional rise in the aging population in Western countries, the rise in clinical interventions, rehabilitation and the increased concerns about quality of life in older adults. Multisensory cues have already been effectively used in cognitive rehabilitation strategies such as the use of visual cues placed near the hand to improve recovery of somesthesis after unilateral brain damage (Rorden, Heutink, Greenfield, & Robertson, 1999). In addition, one may think of technical devices that make greater use of multisensory cues like video telephones. Aging research and MSI may for these reasons be of importance for health care, quality of life, improvement of disabilities and maintenance of functional independence of the elderly.

References

Barutchu, A., Crewther, D. P., & Crewther, S. G. (2009). The race that precedes coactivation: Development of multisensory facilitation in children. *Developmental Science, 12*(3), 464-473. doi: 10.1111/j.1467-7687.2008.00782.x

Birren, J. E., & Fisher, L. M. (1995). Aging and speed of behavior: Possible consequences for psychological functioning. *Annu Rev Psychol, 46*, 329-353. doi: 10.1146/annurev.ps.46.020195.001553

Busey, T., Craig, J., Clark, C., & Humes, L. (2010). Age-related changes in visual temporal order judgment performance: Relation to sensory and cognitive capacities. *Vision Research, 50*(17), 1628-1640. doi: 10.1016/j.visres.2010.05.003

Bäckman, L., Nyberg, L., Lindenberger, U., Li, S. C., & Farde, L. (2006). The correlative triad among aging, dopamine, and cognition: current status and future prospects. *Neurosci Biobehav Rev, 30*(6), 791-807. doi: 10.1016/j.neubiorev.2006.06.005

Cabeza, R., Daselaar, S. M., Dolcos, F., Prince, S. E., Budde, M., & Nyberg, L. (2004). Task-independent and task-specific age effects on brain activity during working memory, visual attention and episodic retrieval. *Cereb Cortex, 14*(4), 364-375.

Corso, J. F. (1971). Sensory processes and age effects in normal adults. *J Gerontol, 26*(1), 90-105.

Craig, J. C., Rhodes, R. P., Busey, T. A., Kewley-Port, D., & Humes, L. E. (2010). Aging and tactile temporal order. *Atten Percept Psychophys, 72*(1), 226-235. doi: 10.3758/APP.72.1.226

Diaconescu, A. O., Hasher, L., & McIntosh, A. R. (2013). Visual dominance and multisensory integration changes with age. *Neuroimage, 65*, 152-166. doi: 10.1016/j.neuroimage.2012.09.057

Diederich, A., Colonius, H., & Schomburg, A. (2008). Assessing age-related multisensory enhancement with the time-window-of-integration model. *Neuropsychologia, 46*(10), 2556-2562. doi: 10.1016/j.neuropsychologia.2008.03.026

Foxe, J. J., & Molholm, S. (2009). Ten years at the multisensory forum: Musings on the evolution of a field. *Brain Topography, 21*, 149-154.

Gori, M., Del Viva, M., Sandini, G., & Burr, D. C. (2008). Young children do not integrate visual and haptic form information. *Curr Biol, 18*(9), 694-698. doi: 10.1016/j.cub.2008.04.036

Grady, C. L. (2008). Cognitive neuroscience of aging. *Ann N Y Acad Sci, 1124*, 127-144. doi: 10.1196/annals.1440.009

Habak, C., & Faubert, J. (2000). Larger effect of aging on the perception of higher-order stimuli. *Vision Research, 40*(8), 943-950. doi: 10.1016/s0042-6989(99)00235-7

Hillock-Dunn, A., & Wallace, M. T. (2012). Developmental changes in the multisensory temporal binding window persist into adolescence. *Developmental Science, 15*(5), 688-696. doi: 10.1111/j.1467-7687.2012.01171.x

Keetels, M., & Vroomen, J. (2005). The role of spatial disparity and hemifields in audio-visual temporal order judgments. *Experimental Brain Research, 167*, 635-640.

Keller, B. K., Morton, J. L., Thomas, V. S., & Potter, J. F. (1999). The effect of visual and hearing impairments on functional status. *Journal of the American Geriatrics Society, 47*(11), 1319-1325.

Kwakye, L. D., Foss-Feig, J. H., Cascio, C. J., Stone, W. L., & Wallace, M. T. (2011). Altered auditory and multisensory temporal processing in autism spectrum disorders. *Frontiers in integrative neuroscience, 4*, 129.

Laurienti, P. J., Burdette, J. H., Maldjian, J. A., & Wallace, M. T. (2006). Enhanced multisensory integartion in older adults. *Neurobiology of aging, 27*, 1155-1163.

Mahoney, J. R., Verghese, J., Dumas, K., Wang, C. L., & Holtzer, R. (2012). The effect of multisensory cues on attention in aging. *Brain Research, 1472*, 63-73. doi: 10.1016/j.brainres.2012.07.014

Massaro, D. W. (1984). Children's perception of visual and auditory speech. *Child Dev, 55*(5), 1777-1788.

McGurk, H., & MacDonald, J. (1976). Hearing lips and seeing voices. *Nature, 264*, 746-748.

Morein-Zamir, S., Soto-Faraco, S., & Kingstone, A. (2003). Auditory capture of vision: Examining temporal ventriloquism. *Cognitive brain research, 17*, 154-163.

Mozolic, J. L., Hayasaka, S., & Laurienti, P. J. (2010). A cognitive training intervention increases resting cerebral blood flow in healthy older adults. *Frontiers in Human Neuroscience, 4*. doi: 10.3389/neuro.09.016.2010

Mozolic, J. L., Hugenschmidt, C. E., Peiffer, A. M., & Laurienti, P. J. (2012). Multisensory integration and aging. In M. M. Murray & M. T. Wallace (Eds.), *The neural bases of multisensory processes.* Boca Raton (FL), USA: CRC Press.

Nardini, M., Jones, P., Bedford, R., & Braddick, O. (2008). Development of cue integration in human navigation. *Curr Biol, 18*(9), 689-693. doi: 10.1016/j.cub.2008.04.021

Nusbaum, N. J. (1999). Aging and sensory senescence. *Southern Medical Journal, 92*(3), 267-275.

Peiffer, A. M., Mozolic, J. L., Hugenschmidt, C. E., & Laurienti, P. J. (2007). Age-related multisensory enhancement in a simple audiovisual detection task. *Neuroreport, 18*(10), 1077-1081. doi: 10.1097/WNR.0b013e3281e72ae7

Poliakoff, E., Shore, D. I., Lowe, C., & Spence, C. (2006). Visuotactile temporal order judgments in ageing. *Neuroscience Letters, 396*(3), 207-211. doi: 10.1016/j.neulet.2005.11.034

Rhodes, M. G. (2004). Age-related differences in performance on the Wisconsin card sorting test: A meta-analytic review. *Psychol Aging, 19*(3), 482-494. doi: 10.1037/0882-7974.19.3.482

Rorden, C., Heutink, J., Greenfield, E., & Robertson, I. H. (1999). When a rubber hand 'feels' what the real hand cannot. *Neuroreport, 10*(1), 135-138.

Scheier, C. R., Nijhawan, R., & Shimojo, S. (1999). Sound alters visual temporal resolution. *Investigative ophthalmology and visual science, 40*, 4169.

Setti, A., Finnigan, S., Sobolewski, R., McLaren, L., Robertson, I. H., Reilly, R. B., . . . Newell, F. N. (2011). Audiovisual temporal discrimination is less efficient with aging: An event-related potential study. *Neuroreport, 22*(11), 554-558. doi: 10.1097/WNR.0b013e328348c731

Shore, D. I., Burack, J. A., Miller, D., Joseph, S., & Enns, J. T. (2006). The development of change detection. *Developmental Science, 9*(5), 490-497. doi: 10.1111/j.1467-7687.2006.00516.x

Stekelenburg, J. J., & Vroomen, J. (2005). An event-related potential investigation of the time-course of temporal ventriloquism. *Neuroreport, 16*, 641-644.

Stephen, J. M., Knoefel, J. E., Adair, J., Hart, B., & Aine, C. J. (2010). Aging-related changes in auditory and visual integration measured with MEG. *Neuroscience Letters, 484*(1), 76-80. doi: 10.1016/j.neulet.2010.08.023

Virsu, V., Lahti-Nuuttila, P., & Laasonen, M. (2003). Crossmodal temporal processing acuity impairment aggravates with age in developmental dyslexia. *Neuroscience Letters, 336*(3), 151-154. doi: 10.1016/s0304-3940(02)01253-3

Vroomen, J., & De Gelder, B. (2004). Temporal ventriloquism: Sounds modulates the flash-lag effect. *Journal of experimental psychology: Human perception and performance, 30*(3), 513-518.

Vroomen, J., & Keetels, M. (2006). The spatial constraint in intersensory pairing: No role in temporal ventriloquism. *Journal of Experimental Psychology: Human Perception and Performance, 32*(4), 1063-1071.

Wallace, M. (2004). The development of multisensory integration. In G. A. Calvert, C. Spence & B. E. Stein (Eds.), *The handbook of multisensory processes* (pp. 625-642). Cambridge MA: MIT.

Weiss, A. D. (1963). Auditory perception in relation to age. In J. E. Birren, R. N. Butler, S. W. Greenhouse, L. Sokoloff & M. R. Yarrow (Eds.), *Human aging: A biological and behavioral study* (pp. 111-140). Bethesda, MD, US: United States Department of Health, Education and Wealthfare.

Zampini, M., Shore, D. I., & Spence, C. (2003). Audiovisual temporal order judgments. *Experimental Brain Research, 152*(2), 198-210. doi: 10.1007/s00221-003-1536-z

Chapter 7

Summary and general discussion

The general aim of this thesis was to contribute to the knowledge on audiovisual integration of low-level information in people with Autism Spectrum Disorders (ASD), schizophrenia, dyslexia and in the elderly. Existing literature on multisensory integration (MSI) in ASD and schizophrenia is limited and focuses mainly on the integration of higher-order stimuli, like speech and emotions. In addition, findings are not always consistent (e.g., Bebko, Weiss, Demark, & Gomez, 2006; De Gelder, Vroomen, & Van der Heide, 1991; Foucher, Lacambre, Pham, Giersch, & Elliott, 2007; Magnée, Oranje, Van Engeland, Kahn, & Kemner, 2009; Peled, Ritsner, Hirschmann, Geva, & Modai, 2000; Williams, Massaro, Peel, Bosseler, & Suddendorf, 2004). Furthermore, Hairston, Burdette, Flowers, Wood & Wallace (2005) suggest that research in developmental dyslexia has shown that the integration of audiovisual information is undoubtedly a critical process in the development of linguistic skills (especially reading). Related to this, their Temporal Order Judgment (TOJ) study on people with dyslexia showed altered crossmodal temporal processing. Unfortunately, MSI research in dyslexia is still a quite unreclaimed area of research, but findings as by Hairston et al. (2005) should be further explored to contribute to the knowledge on MSI in dyslexia. Finally, from a developmental perspective on MSI, the effect of aging on audiovisual integration was also examined. As most developmental evidence comes from studies on infants and children (e.g., Barutchu, Crewther, & Crewther, 2009; Massaro, 1984), studies in the elderly could provide complementary knowledge on this topic. Therefore, MSI was studied in various age groups (20-, 30-, 40-, 50- and 60-year-olds) to examine possible (audiovisual) integration differences related to age.

Summary of the results

In the studies of this thesis, a visual TOJ task was used to examine low-level audiovisual integration in people with ASD, schizophrenia and in people in various age groups. In this task, participants judged which of two flashes appeared first. In 'healthy' controls, sensitivity to visual temporal order improves when two click sounds are added, one before the first flash and one after the second flash, because the apparent perceived Stimulus Onset Asynchrony (SOA) between the two flashes is increased (temporal ventriloquism effect). A visual TOJ task was used in this thesis to examine whether this temporal ventriloquism effect (TVE) was also present in the 'study groups'. The effect of sound on visual search and orienting was examined with the 'pip-and-pop' visual search task in individuals with dyslexia and ASD. In this task, a visual target (a horizontal or vertical line) is embedded in a cluttered display of distracters (oblique lines). The targets and distracters change, on randomly determined times, color from green-to-red or red-to-green. The search time can be drastically improved when a 'pip'-sound is synchronized with the color-change of the target: the 'pip' then makes the target 'pop-out'. Interestingly, the results of these studies are overall unambiguous across the different 'study groups', as the presence of sounds in the visual TOJ task as well as in the 'pip-and-pop' task increased – or, in some cases, 'restored'– the visual performance of the 'study groups'.

The 'study groups' who performed on the visual TOJ task (people with ASD, schizophrenia and the aging groups) showed overall diminished sensitivity to visual temporal order compared to their control group (the 'study groups' showed larger Just Noticeable Differences (JNDs), i.e., they needed more time between the visual stimuli to correctly judge their temporal order). However, the integration of low-level audiovisual stimuli in these individuals was intact, as their sensitivity to visual temporal order improved substantially when click sounds were added to the task (their JNDs decreased) (**Chapters 2**, **4** and **6**). Additional research in adolescents with ASD, using an audiovisual TOJ task, showed that the adolescents also had difficulties judging audiovisual synchrony (**Chapter 3**). The findings of these two TOJ tasks suggest that adolescents with ASD have specific impairments of (audio)visual temporal sensitivity for synchrony or order.

The individuals with ASD and dyslexia who performed on the 'pip-and-pop' task also profited from the presence of sound, as their visual search time improved when a click sound, presented in synchrony with a color change of the target, was added to the task (**Chapter 4** and **5**). In case of the adolescents with ASD, their overall performance on this task did not significantly differ from that of the control group, as their visual search performance in both the sound absent and the sound present condition was comparable with those of their control group. Together with our findings of additional research on visual attentional shifting and/or disengagement in adolescents with ASD, we found no evidence of impaired visual search and orienting (**Chapter 4**) in this group. The dyslexic readers, however, were generally slower than the normal readers in their search for the target. The addition of the click sound, though, drastically improved their performance up to the level of the normal readers (**Chapter 5**).

In sum, our results show that visual performance of all 'study groups' improved, at least by equal amounts as in the control groups, when sounds are added to the visual TOJ task and the 'pip-and-pop' task. As stated before, the visual search performance of the dyslexic readers improved even more than in the control group, resulting in visual search times that were eventually comparable to those of the control group. The beneficial effect of sounds has already been shown in many studies with 'healthy' controls (e.g., Doyle & Snowden, 2001; Keetels & Vroomen, 2005, 2011; Morein-Zamir, Soto-Faraco, & Kingstone, 2003; Scheier, Nijhawan, & Shimojo, 1999; Van der Burg, Olivers, Bronkhorst, & Theeuwes, 2008b). The results of this thesis now show that this beneficial sound effect is also present in individuals with ASD, schizophrenia and dyslexia, and in people in various age groups. Based on the findings of this thesis, one could even suggest that sounds may have a 'rehabilitating' effect on the visual performance of the 'study groups' who participated in this thesis, as sounds, in some cases, 'repair' the reduced visual performance up to the level of 'healthy' controls. Based on these findings, three important questions arise; (1) why is sensitivity to (audio)visual temporal order reduced, (2) why do sounds have such a beneficial effect on visual processing in the 'study groups' and (3) why is visual search time *in people with dyslexia reduced (and not in adolescents with ASD)?*

In the next paragraphs, possible answers to these questions will be discussed. First, the role of attention will be described with focus on attention and visual processing, the attentional role of sound and the relation between attention and MSI. Then, suggested impairments in temporal processing in the 'study groups' will be discussed. At last, a developmental perspective on MSI will be discussed.

Before moving on to the next paragraph, this discussion would not be complete without a schematic overall view of the results on how the different 'study groups' performed on similar tasks in relation to each other and their control groups. Therefore, Tables 1 and 2 provide an overview, per task, of how the different 'study groups' performed. For methodological reasons, such as different audiovisual conditions that were used in the visual TOJ task between the 'study groups', varying numbers of participants per group and level of fatigue caused by different test batteries, no conclusions are drawn on these data at this stage.

Table 1. Mean Just Noticeable Differences (in ms) in Visual-only Condition and at Audio-visual Intervals of ~0 ms and ~100 ms for each 'Study Group' and their 'Control Group' that participated in the Visual TOJ Task, including Mean Effect of Sound and Mean Temporal Ventriloquism Effect (TVE) per Group

	Visual only	~0 ms	~100 ms	Sound effect	TVE
Adolescents with ASD	38.2	26.5	24.9	11.7	1.6
Adults with schizophrenia	39.6	25.7	21.5	14.0	4.1
50- and 60-year-olds	42.6	36.0	28.6	6.7	7.3
	Visual only	~0 ms	~100 ms	Sound effect	TVE
Control group ASD	25.2	21.4	20.7	3.8	0.6
Control group schizophrenia	28.5	21.1	18.1	7.5	3.0
20- and 30-year-olds[1]	26.9	25.1	24.7	1.8	0.4

Table 2. Mean Search Time (in s) per Combination of Sound Condition and Set Size for the Adolescents with ASD and Adults with Dyslexia (upper panel) and their Control Group (lower panel)

	Set size 24			Set size 48		
	No sound	Sound	Sound effect	No sound	Sound	Sound effect
Adolescents with ASD	2.0	2.4	-0.4	5.4	4.5	0.9
Adults with dyslexia	5.7	4.7	1.0	13.2	8.4	3.8
	Set size 24			Set size 48		
	No sound	Sound	Sound effect	No sound	Sound	Sound effect
Control group ASD	4.2	3.7	0.5	8.9	6.8	2.1
Control group dyslexia	4.5	4.2	0.3	8.4	7.4	1.0

[1] In the aging study different age groups were compared with each other. This study set up differed from the other studies in which 'study groups' were compared with age-gender matched control groups. To make a study-control group comparison as in the ASD and schizophrenia study, the 40-year-olds were not included in the comparison, as it is not clear whether they belong to 'the young' or 'the older'.

The role of attention

Attention and visual processing

First, the role of attention on the visual performance of the 'study groups' will be discussed here. There is a substantial amount of empirical evidence about the presence of (visual) attentional problems in people with ASD, schizophrenia and dyslexia, and in people who are aging (e.g., Alain & Woods, 1999; Brannan & Williams, 1987; Courchesne et al., 1994; Neuchterlein, Dawson, Ventura, Miklowitz, & Konishi, 1991). Considering the nature of these problems and our findings of reduced visual performance in our 'study groups', it is interesting to take a closer look at the attentional mechanisms in the 'study groups' and the possible relation to our findings.

ASD studies on the orientation of attention have shown that people with ASD typically suffer from impairments in the shifting of attention (Akshoomoff & Courchesne, 1992; Courchesne et al., 1994; Wainwright-Sharp & Bryson, 1993). In their review, Allen and Courchesne (2001) argue that people with ASD tend to show an abnormal distribution of attentional resources across space with impairments of re-allocating attentional resources to new spatial locations. Such attentional abnormalities could impair the ability to perceive visual transient stimuli for which an attentional shift is required. This hypothesis fits with the results of Chapter 4, where reduced sensitivity to visual temporal order in adolescents with ASD on the visual TOJ task was reported.

Abnormalities of attention and visual perception are also considered core features of the cognitive dysfunction associated with schizophrenia (Fioravanti, Carlone, Vitale, Cinti, & Clare, 2005; McGhie & Chapman, 1961; Neuchterlein et al., 1991; Posner, Early, Reiman, Pardo, & Dhawan, 1988). Additionally, though evidence may not be as overwhelming as in ASD, findings are reported that individuals with schizophrenia have problems with the shift of attention as well (Carter et al., 2010; Posner et al., 1988; Potkin, Swanson, Urbanchek, Carreon, & Bravo, 1989). For example, results from a recent fMRI-study by Carter et al. (2010) made the authors suggest that attentional deficits displayed by patients with schizophrenia may reflect deficits in modulating brain activity in response to variations in transient, attentional demanding stimuli. Presumably, these findings can affect the ability to perceive the visual transient stimuli as used in the visual TOJ task. This is in line with findings of Chapter 2, in which sensitivity to visual temporal order in people with schizophrenia is diminished.

In our dyslexia study, we found more direct evidence for a possible relation between attentional deficits and visual processing performance. According to the 'Sluggish Attentional Shifting' (SAS) hypothesis by Hari and Renvall (2001), sensory input is chunked in dyslexic readers by which their attention, once engaged on a chunk, cannot be easily disengaged. This causes impairments in the shift or the focusing of attention. In line with the SAS hypothesis, our results showed that the dyslexic readers were generally slower than normal readers in their visual search time of a horizontal or vertical target among oblique distracters (Chapter 5) in the no-sound condition. Following SAS, this is caused by the dyslexic readers' automatic attention system that cannot disengage fast enough to move from one item to the next. This resulted in a prolonged dwell time. These findings may provide evidence that problems with the shifting or disengagement of attention have an adversely affect on visual processing.

Results from visual TOJ studies in people with dyslexia showed that dyslexic readers also performed worse, compared to normal readers, on the judgment of visual temporal order (i.e., less sensitive) (Hari, Renvall, & Tanskanen, 2001; Jáskowski & Rusiak, 2008; Liddle et al., 2009). For example, Liddle et al. (2009) investigated dyslexic readers on visual TOJ tasks that allowed the authors to measure both sensitivity to temporal order and spatial attentional bias. They found not only that dyslexic readers were significantly less sensitive to visual temporal order, but also that attentional deficit symptoms impaired their temporal processing at short SOAs. This made the authors conclude that people with attentional deficits find a visual TOJ task difficult when the stimuli are presented rapidly, even in the absence of a phonological deficit. These findings, together with our results from the 'pip-and-pop' study, might also provide strong evidence for a relation between attentional problems and diminished sensitivity to visual temporal order or visual processing more generally.

Finally, selective attention is of particular relevance to aging. Selective attention is a top-down control mechanism that allows us to focus on a particular location, stimulus feature, or sensory modality while ignoring other possible options (Corbetta, Miezin, Dobmeyer, Shulman, & Petersen, 1990; Kastner & Ungerleider, 2000; Posner & Driver, 1992; Spence & Driver, 1997; Spence, Nicholls, & Driver, 2001). There is strong evidence that older adults can, in fact, successfully engage selective attention on a variety of tasks (Groth & Allen, 2000; Madden, Whiting, Cabeza, & Huettel, 2004; Townsend, Adamo, & Haist, 2006; Verhaeghen & Cerella, 2002) and that by attending to a single sensory modality older adults can reduce MSI (Hugenschmidt, Mozolic, & Laurienti, 2009). These findings do not fit with the results of our aging study, as we found diminished sensitivity for visual temporal order in the older age groups, instead of enhanced visual performance (as would be expected according to successful engagement of selective attention). The reduced sensitivity for visual temporal order as seen in the 50- and 60-year-olds in our study can thus not be directly explained by attentional shifting or disengagement impairments in the elderly as it might do in the other 'study groups'. Future research is needed to further examine underlying mechanisms like general slowing in the elderly or a reduction in the size of older adult's functional visual field (Cerella, 1985) that could account for the reduced visual performance in the elderly.

Based on the empirical evidence of attentional impairments reported in ASD, schizophrenia and dyslexia and related to the findings of our studies, it is suggested that attentional shifting and/or disengagement problems might contribute to diminished visual processing. However, our results from the 'pip-and-pop' study with adolescents with ASD do not show evidence of reduced visual search time (in both the sound-absent and sound-present condition) and deviate, in this case, from the findings in the dyslexic readers. Obviously, these results conflict with the hypothesis on a possible relation between impaired visual attention and reduced visual processing. Although, in this stage of our research it is not quite clear what causes this difference, it might be suggested that the discrimination between attentional shifting and disengagement problems might play a crucial role here. Evidence on attentional impairments in individuals with ASD mainly focus on shifting problems, as the SAS hypothesis by Hari and Renvall (2001) assumes that attentional disengagement is the main problem in dyslexia. Another (speculative) explanation might be that individuals with dyslexia have more difficulty to narrow their attentional focus and therefore tend to adopt a more distributed focus of attention (Facoetti, Paganoni, & Lorusso, 2000). On the contrary, individuals with ASD tend to show detail-focused local processing (Frith, 1989) which may have been beneficial in the visual search in the no-sound condition. Elaborated and future research on this topic should shed more light on underlying explanations. However, I do suggest the possibility that deficits with the shifting and/or disengagement of attention may underlie reduced visual processing.

Attention and sound

As findings of our 'pip-and-pop' task in people with dyslexia and ASD show, the visual performance of the groups improved significantly when a 'pip'-sound was synchronized with the color-change of the target. Van der Burg et al. (2008b) explained this phenomenon arguing that the binding of synchronized auditory-visual signals occurs rapidly, automatically, and effortless, with the auditory signal attaching to the visual signal relatively early in the perceptual process. This way, a non-spatial auditory event ('pip') can guide attention towards the location of a synchronized visual event that, without an auditory signal, is difficult (Van der Burg et al., 2008b). The 'pip' then makes the target 'pop-out', changing a serial search into an automatic, parallel search, which results in reduced visual (target-item) search times. With our 'pip-and-pop' studies in people with dyslexia and ASD, we are one of the first to show that the 'pip-and-pop' effect also exists in people with ASD and dyslexia and that the presence of sound thus can have a beneficial effect on visual attention in these individuals. This assumption also fits our findings on the visual TOJ studies, together with the hypothesis that attentional problems may account for diminished sensitivity to visual temporal order. The presence of sound attracts the visual attention of the participants in the 'study groups', leading to improved judgments on visual temporal order.

Elaborating on the SAS hypothesis that impaired attentional disengagement might cause reduced visual search times in dyslexic readers in the no-sound condition of the 'pip-and-pop' task, the finding that the presence of sound lifts the performance of the dyslexic readers up to the level of the normal readers, suggests that sound may (even) compensate for attentional disengagement problems in dyslexia.

Previous studies on the effects of simple auditory sounds already suggested that an auditory signal may promote attentional disengagement (e.g., Doyle & Snowden, 2001; Keetels & Vroomen, 2011). In their study, Keetels and Vroomen (2011) examined the effects of a task-irrelevant sound on visual processing and found that an early sound can speed-up the velocity of the attentional shift towards the target. These results together – better disengagement and faster shifting – fit our findings and provide even more *evidence for the suggestion that sounds can have beneficial and facilitating effects on* (visual) attention.

At last, one can ask to which extent the beneficial effect of sounds on both sensitivity to visual temporal order and visual search time might be triggered by an alerting effect. For example, Robertson, Mattingley, Rorden & Driver (1998) studied patients with neglect and showed that phasic alerting by a transient non-spatial sound can overcome their spatial deficits in visual awareness. This finding provides evidence that phasic alerting alone can directly affect the speed of perceptual processing, rather than merely affecting motor readiness. Follow-up studies by Van der Burg, Talsma, Olivers, Hickey, & Theeuwes (2011) and Van der Burg, Olivers, Bronkhorst, & Theeuwes (2008a), however, found evidence for a very early multisensory interaction that ruled out that the 'pip-and-pop' effect is due to increases of alertness, as the effect follows a time course that is quite different from alerting effects. In addition, a study by Morein-Zamir et al. (2003) investigated the effect of phasic alerting as an explanation for the temporal ventriloquism effect, using a visual TOJ task in which the first sound could appear at the same time as the first light or lead by 100 ms. Similarly, the second sound could appear at the same time as the second light, or trail by 100 ms. Their results ruled out an alerting explanation, as TOJ performance improvement was due to the presentation of the second sound after the second light and presenting a sound before the first light did not improve performance relative to the visual-only condition. In terms of temporal ventriloquism, the second sound thus biases the onset of the second light and intact audiovisual integration is required for this effect to occur. Finally, Keetels and Vroomen (2011) also suggested that it is unlikely that the sound used in their tasks acted as a general temporal warning signal for when to expect the cue or when to shift attention, because a visual signal with the same timing information as the sound had a very different effect on latency. Although these results provide incriminating evidence for a phasic alerting effect of sound in our studies, the phasic alerting effect is not ruled out in this thesis, as there have been no follow-up studies on our results to examine the role of this phenomenon (like in the Keetels & Vroomen (2011) and Van der Burg et al. (2011) studies). Future research should shed more light on this issue in these 'study groups'.

Attention and MSI

A final remark on the role of attention is the ongoing discussion in the current literature about whether attention is a prerequisite for MSI to occur, or that MSI occurs relatively easy and automatic and appears to affect the allocation of attention. For example, at low pre-attentive levels, MSI can automatically capture attention, which is for instance shown in the 'pip-and-pop' study by Van der Burg et al. (2008a), in which visual objects are faster detected when auditory signals were added to the task. Our findings on the visual TOJ tasks show that, although (visual) attentional impairments are reported in all our 'study groups', these impairments have had no adverse effect on the low-level audiovisual integration in our studies, as this was intact in all groups. These results seem consistent with the claim that the low-level audiovisual integration precedes attentional selection and that low-level audiovisual integration operates in a pre-attentional fashion (Talsma, Doty, & Woldorff, 2007).

Impaired temporal processing

Besides attentional impairments, there is also evidence of temporal processing deficits in ASD, schizophrenia, dyslexia and aging. For example in dyslexia, many studies report empirical evidence of temporal processing deficits in the auditory, but also visual modality (DiLollo, Hanson, & McIntyre, 1983; Farmer & Klein, 1995; Hairston et al., 2005; Laasonen, Service, & Virsu, 2002; May, Williams, & Dunlap, 1988). These results even led to the formulation of the 'temporal processing deficit' theory in dyslexia, which states that the dysfunction on the speech level is due to general difficulties in processing of information entering the sensory systems in rapid succession. Results from studies in schizophrenia suggest that the disorder is associated with a fundamental disturbance in the temporal coordination of information processing in the brain leading to dysfunctions in the timing of perceptual, cognitive and motor processes, and disturbances of consciousness (e.g., Andreasen, Paradiso, & O'Leary, 1998; Bressler, 2003; Paulus & Braff, 2003).

Temporal processing deficits may lead to a variety of abnormalities, for example, difficulties in reproducing auditory stimulus durations in ASD (Szelag, Kowalska, Galkowski, & Pöppel, 2004), higher auditory sensitivity thresholds in children with ASD (Kwakye, Foss-Feig, Cascio, Stone, & Wallace, 2011), less temporal precision in the perception of auditory durations in schizophrenia (Carroll, Boggs, O'Donnell, Shekhar, & Hetrick, 2008) and a reduced ability to discriminate the visual temporal order of two visual stimuli in dyslexia (e.g., Jáskowski & Rusiak, 2008). Given these findings, it seems presumable to suggest that the sensitivity of visual temporal order in our studies is affected by temporal processing impairments.

Some of the above-mentioned studies suggest that unisensory temporal processing deficits also lead to altered temporal MSI. For example, Kwakye et al. (2011) reported that children with ASD showed enlarged windows of temporal integration and Hairston et al. (2005) suggested an extended temporal window for binding visual and auditory cues in individuals with dyslexia. In our visual TOJ studies, we found no evidence of an enlarged temporal window of integration as individuals with ASD, schizophrenia and the elderly showed equal amounts of temporal ventriloquism effect (TVE) compared to the controls groups and showed no enhanced TVE on the larger audiovisual delays (i.e., on the ~200 and ~300 ms audiovisual lags). However, our audiovisual TOJ study in adolescents with ASD showed that the adolescents were less sensitive to the temporal order of audiovisual stimuli, suggesting that adolescents with ASD may suffer from a general impairment in audiovisual temporal processing. Quite similar results were observed in the audiovisual TOJ task in our aging study, in which the 60-year-olds were found to be the least sensitive to audiovisual temporal order. This study also showed that sensitivity to audiovisual temporal order does not appear to be a good predictor of MSI, as the 60-year-olds showed enhanced – rather than diminished – MSI as an effect of aging. To conclude, the integration of low-level audiovisual stimuli in individuals with ASD, schizophrenia and the elderly was comparable with that of their control groups, suggesting no impairment in low-level MSI. In the elderly and the adolescents with ASD, there might be evidence for altered multisensory temporal function. However, our results indicate that the unisensory temporal processing impairments which may cause diminished sensitivity to visual temporal order, might be 'restored' by the presence of sound.

As a final remark, many studies on TVE in 'healthy' participants have demonstrated that vision is somewhat flexible on the time dimension and the perceived timing of a visual event is – within limits – attracted towards other events in audition (and touch) (e.g., Keetels & Vroomen, 2005, 2008). According to our findings, it might be possible that this flexible visual mechanism is (still) present in, at least, people with ASD and schizophrenia and the elderly as well.

A developmental perspective on MSI

At last, we discuss some developmental issues that could be related to our findings, and which may also be associated with the conflicting results in the literature on MSI in ASD, schizophrenia, dyslexia and aging. As our aging study shows, the deterioration of unisensory visual and auditory temporal sensitivity occurs at least by the age of 60 years, but MSI is not diminished in the elderly and can even serve as a compensatory mechanism that diminishes the adverse effects of aging. These findings raised questions about possible developmental issues in MSI and its impact on the findings of the studies in this thesis.

Clearly, as we age, there are significant changes in all our sensory systems. There are also a variety of cognitive functions and widespread changes in the aging brain, like increased hearing thresholds, declines in motor speed, executive function and memory (Birren & Fisher, 1995; Rhodes, 2004) and alterations in neurotransmitter systems (Bäckman, Nyberg, Lindenberger, Li, & Farde, 2006). Taking these age-related changes in brain structures and systems and alterations in perception, sensation and cognition altogether, it seems only natural that this could have its impact on MSI in aging as well. On the other hand, there is convincing evidence from prospective developmental studies that intersensory integration already occurs in early development and that multisensory perception emerges in its various forms during the first years of life (e.g., Lewkowicz, 1996; Lickliter & Bahrick, 2000). For example, a recent study by Hillock-Dunn and Wallace (2012) reported changes in audiovisual temporal processing from early childhood through early adulthood and provides evidence that differences in the perception of multisensory temporal relations persist well into adolescence. These findings could, for example, account for the conflicting results on MSI in individuals with ASD, as results of studies with children are compared to those of adults and vice versa. It could also explain why we did not find any evidence for an enlarged temporal window of integration in adolescents with ASD and the study by Kwakye et al. (2011) on children with ASD did.

It may seem obvious that developmental brain changes are not only present in the 'healthy' brain, but also (or even more) in the 'disordered' brain. Although we will not discuss this topic in details, we will describe a proposition made by Uhlhaas and Singer (2010) on a developmental mechanism of the schizophrenia brain as an example. These authors hypothesize that in schizophrenia abnormal temporal dynamics of cortical circuits may result in impairments in synaptic plasticity. Impaired plasticity is a candidate mechanism for the enduring cognitive deficits and aberrant neurodevelopment observed in schizophrenia, and there is evidence that neural oscillations and asynchrony may have a crucial role in synaptic modifications. As behavioral impairments are already detectable in children who develop schizophrenia at a later stage in life, dysfunctional neural oscillations and plasticity are likely to cause aberrant early pre- and perinatal development, leading to maladaptive formation of cortical networks and faulty programming of synaptic connections. Accordingly, the authors propose that this fundamental impairment remains silent until the late adolescent period when cortical networks fully exploit neural oscillations for the coordination of distributed brain processes.

The results discussed in this paragraph on developmental perspectives on MSI as well as on the anatomy and physiology of the (disordered) brain indicate that the developmental trajectory of the brain may have played an influential role in our studies (especially the aging and ASD studies), as well as in the conflicting results in the literature on MSI in different groups of individuals.

Methodological considerations

We realize that the studies in this thesis are restricted to some limitations. Consequently, generalizations of our results should be made carefully and several methodological considerations should be made.

As becomes clear from the previous paragraph, a caveat of our results is that they need to be put in a developmental perspective. The participants in our 'study groups' varied per study, from (mainly) adolescents and young adults, to adults, middle-aged and more elderly people. Furthermore, in the ASD studies, we only examined a very specific group of high-functioning individuals without intellectual disabilities and also in the schizophrenia study we investigated adults with normal intelligence and good task comprehension. Considering these characteristics of the participants in the ASD and schizophrenia group, the results of these studies may not be applicable to other clinical subpopulations such as children and adults with ASD and/or lower-functioning individuals with ASD or schizophrenia. For example, compensatory mechanisms may develop over time, which makes it harder to detect perceptual anomalies in adults with ASD, especially those who are high functioning. Finally, some of the participants in the ASD and schizophrenia studies were on (antipsychotic) medication and it is not clear to what extent drug treatment has affected our results. Interestingly, several studies observed visual processing deficits using behavioral measures in both medicated and non-medicated individuals with schizophrenia (Braff & Saccuzzo, 1982; Brody, Saccuzzo, & Braff, 1980; Butler et al., 2003; Butler, Harkavy-Friedman, Amador, & Gorman, 1996; Harvey et al., 1990), as well as in first-degree relatives of people with schizophrenia (Chen, Nakayama, Levy, Matthysse, & Holzman, 1999; Green, Nuechterlein, & Breitmeyer, 1997; Kéri & Janka, 2004) and in people with schizotypical personality disorder (Braff, 1981) who were not on medication. Although these studies provide evidence for a diminished drug effect on visual processing performance, it remains for future studies to examine whether our results can be generalized to non-medicated individuals with ASD and schizophrenia, as an effect of drug treatment cannot be ruled out at this stage.

To conclude, given these limitations on our studies, additional research will have to consider how visual temporal processing, visual attention and low-level audiovisual integration varies across subpopulations within each disorder and how individuals within these groups relate to people with typical development and/or to those who are both developmentally impaired but non-autistic.

Future research

Based on the methodological considerations, as discussed in the previous paragraph, we suggest that there should be more focus on the developmental aspects of MSI and brain structures in the 'study groups'. Sensory difficulties might be present early on during development, but possibly fade away with age, due to several mechanisms. Prospective developmental studies on MSI in ASD would be interesting to gain more insights in the developmental changes in the autistic brain and would also be of great value in the (ongoing) debate in the literature on impaired versus intact audiovisual integration in this disorder. This could be realized, for example, by longitudinal research on MSI in ASD starting with children and continue into adulthood and even aging. Another option is to use similar tasks in different age groups (for example, children, adolescents, adults and elderly with ASD compared to age-matched controls). Furthermore, aging and MSI in 'healthy' individuals should also be further explored in the future, especially given the proportional rise in the aging population in Western countries. As further discussed in the next paragraph on clinical implications, aging research and MSI may be of importance, for example, for health care and quality of life.

Research on MSI in ASD and schizophrenia has mainly focused (as in this thesis) on the integration of audiovisual information. This might seem understandable as multisensory temporal processes have been best examined in the audiovisual domain (Powers, Hillock, & Wallace, 2009) and based on the impairments in communication and social interaction which characterize the disorders. Perception of visual and auditory (emotional) stimuli is of particular importance to understand the social intentions of others and intact integration of higher-level and lower-level audiovisual stimuli thus is a necessary condition for appropriate communication. However, to gain more insights in the underlying mechanisms for MSI to occur, research on the integration of other sensory modalities would be of interest as well, like vision and touch or auditory and touch. This area of research would also be interesting for MSI research in the elderly, as more knowledge on these integration mechanisms could be useful for rehabilitation.

At last, it may be of interest to extend our findings to research in other disorders as well, for example, ADHD. A recent study by Donohue, Darling, & Mitroff (2012), examined the relationship between multisensory temporal processing and self-reported symptoms of autism. They found that a stronger bias to perceive auditory stimuli occurring before visual stimuli as simultaneously was associated with greater levels of autistic symptoms. They also found that multisensory processing correlated with symptoms of ADHD, a disorder which is often found to be co-morbid with autism. Given the attentional problems associated with ADHD and our findings of possible beneficial sound effects on (visual) attention, people with ADHD might be an interesting 'study group' in the light of our thesis.

Clinical implications

Although the nature of our research is quite fundamental, this thesis is not complete without some clinical implications of our findings. As we stated in the previous paragraph (and Chapter 6), MSI in the elderly is an interesting societal topic, given the proportional rise in the aging population in Western countries, the rise in clinical interventions, rehabilitation and the increased concerns about quality of life in older adults. As our results indicate, MSI can serve as a compensatory mechanism for reduced visual and auditory temporal processing, which could be used, for example, in cognitive rehabilitation strategies or for technical devices that make greater use of multisensory cues like video telephones. Aging research on MSI, including our study, may for these reasons be of importance for health care, quality of life, improvement of disabilities and maintenance of functional independence of the elderly. Furthermore, our findings of intact low-level audiovisual integration in ASD, schizophrenia and dyslexia might be of use in multisensory strategies that are, for example, employed to remediate the reading skills of dyslexic individuals or might help to improve the knowledge and quality of (the somewhat disputable) sensory integration therapy in ASD.

Hopefully, our findings of the different studies may be of importance in characterizing the sensory pathologies in ASD, schizophrenia, dyslexia and in aging and lead to more sensitive diagnostic instruments and more specific remediation strategies.

Conclusion

In the beginning of this chapter, three overall questions raised from the findings of the different studies in this thesis: (1) why is sensitivity to (audio)visual temporal order reduced in all the 'study groups' that participated in the visual TOJ task, (2) why do sounds have such a beneficial effect on visual processing in all 'study groups', and (3) why is visual search reduced in people with dyslexia (and not in adolescents with ASD)? A short overview of possible answers/explanations to these questions (see Table 3) is given in this last paragraph.

The earlier mentioned description of the schizophrenia brain by Uhlhaas and Singer (2010) shows the complexity of brain structures and mechanisms in the 'disordered', and perhaps also, aging brain. It also makes clear how difficult it is to provide unambiguous explanations or causes for the impaired behavior that is often associated with a disorder, as a variety of mechanisms are at work, leading to various symptoms. We therefore realize that the discussed issues in this chapter are far from complete and that they are not always generally applicable to the different 'study groups' as we have discussed them. However, it goes beyond the scope of this thesis to discuss a variety of possible underlying causes. The items discussed here are in line with the findings of this thesis and it is for future research to gain more insights in the underlying mechanisms and structures of MSI for each separate disorder. Table 3 gives a schematic reproduction of the discussed explanations for the questions as raised from our overall results.

Table 3. Overview of Discussed Questions and Answers on Overall Results

	Attention	**Temporal processing**	**Developmental issues**
Why is sensitivity to (audio)visual temporal order reduced?	Attentional shifting and/or disengagement problems in people with ASD, schizophrenia and dyslexia might contribute to reduced or impaired visual processing, and possibly also to diminished sensitivity to (audio)visual temporal order	Temporal processing deficits are often reported in people with ASD, schizophrenia, dyslexia and in the elderly and these impairments might affect sensitivity to (audio)visual temporal order	Age- (or disorder) related developmental brain changes might cause altered uni- and multisensory processing
Why do sounds have such a beneficial effect on visual processing?	Sound has a facilitating effect on (visual) attention. Assuming that (visual) attention plays an important role in visual processing, this beneficial sound effect might also have its impact on visual processing	The temporal ventriloquism effect as shown in all the 'study groups' is a result of the effect of sounds on visual temporal processing, resulting in improved sensitivity to visual temporal order	
Why is visual search time reduced in people with dyslexia?	People with dyslexia have attentional disengagement problems by which they cannot disengage their attention fast enough to move from one item to the other, resulting in a prolonged dwell time that might not be caused by attentional shifting deficits (as reported in ASD)		

To summarize, the studies in this thesis show three important findings; (1) people with ASD, schizophrenia, dyslexia and the elderly show diminished visual temporal processing in a visual TOJ task and 'pip-and-pop' visual search task, (2) this visual processing deficit may be compensated by sound, as click sounds have a beneficial, or 'rehabilitating', effect on visual temporal processing in all our 'study groups', and (3) given these improvements on visual temporal processing by the presence of sounds, it can be suggested that people with ASD, schizophrenia, dyslexia and the elderly show intact low-level audiovisual integration.

References

Akshoomoff, N. A., & Courchesne, E. (1992). A new role for the cerebellum in cognitive operations. *Behavioral Neuroscience, 106*, 731-738.

Alain, C., & Woods, D. L. (1999). Age-related changes in processing auditory stimuli during visual attention: Evidence for deficits in inhibitory control and sensory memory. *Psychol Aging, 14*(3), 507-519.

Allen, G., & Courchesne, E. (2001). Attention function and dysfunction in autism. *Frontiers in Bioscience, 6*, 105-119.

Andreasen, N. C., Paradiso, S., & O'Leary, D. S. (1998). 'Cognitive dysmetria' as an integrative theory of schizophrenia: A dysfunction in cortical subcortical-cerebellar circuitry? *Schizophrenia Bulletin, 24*(2), 203-218.

Barutchu, A., Crewther, D. P., & Crewther, S. G. (2009). The race that precedes coactivation: Development of multisensory facilitation in children. *Developmental Science, 12*(3), 464-473. doi: 10.1111/j.1467-7687.2008.00782.x

Bebko, J. M., Weiss, J. A., Demark, J. L., & Gomez, P. (2006). Discrimination of temporal synchrony in intermodal events by children with autism and children with developmental disabilities without autism. *Journal of Child Psychology and Psychiatry, 47*(1), 88-98.

Birren, J. E., & Fisher, L. M. (1995). Aging and speed of behavior: Possible consequences for psychological functioning. *Annu Rev Psychol, 46*, 329-353. doi: 10.1146/annurev.ps.46.020195.001553

Braff, D. L. (1981). Impaired speed of information processing in nonmedicated schizotypal patients. *Schizophr Bull, 7*(3), 499-508.

Braff, D. L., & Saccuzzo, D. P. (1982). Effect of antipsychotic medication on speed of information processing in schizophrenic patients. *Am J Psychiatry, 139*(9), 1127-1130.

Brannan, J. R., & Williams, M. C. (1987). Allocation of visual attention in good and poor readers. *Percept Psychophys, 41*(1), 23-28.

Bressler, S. L. (2003). Cortical coordination dynamics and the disorganization syndrome in schizophrenia. *Neuropsychopharmacology, 28*, S35-S39. doi: 10.1038/sj.npp.1300145

Brody, D., Saccuzzo, D. P., & Braff, D. L. (1980). Information processing for masked and unmasked stimuli in schizophrenia and old age. *J Abnorm Psychol, 89*(5), 617-622.

Butler, P. D., DeSanti, L. A., Maddox, J., Harkavy-Friedman, J. M., Amador, X. F., Goetz, R. R., . . . Gorman, J. M. (2003). Visual backward-masking deficits in schizophrenia: Relationship to visual pathway function and symptomatology. *Schizophr Res, 59*(2-3), 199-209.

Butler, P. D., Harkavy-Friedman, J. M., Amador, X. F., & Gorman, J. M. (1996). Backward masking in schizophrenia: Relationship to medication status, neuropsychological functioning, and dopamine metabolism. *Biol Psychiatry, 40*(4), 295-298. doi: 10.1016/0006-3223(96)00007-8

Bäckman, L., Nyberg, L., Lindenberger, U., Li, S. C., & Farde, L. (2006). The correlative triad among aging, dopamine, and cognition: Current status and future prospects. *Neurosci Biobehav Rev, 30*(6), 791-807. doi: 10.1016/j.neubiorev.2006.06.005

Carroll, C. A., Boggs, J., O'Donnell, B. F., Shekhar, A., & Hetrick, W. P. (2008). Temporal processing dysfunction in schizophrenia. *Brain Cogn, 67*(2), 150-161. doi: 10.1016/j.bandc.2007.12.005

Carter, J. D., Bizzell, J., Kim, C., Bellion, C., Carpenter, K. L. H., Dichter, G., & Belger, A. (2010). Attention deficits in schizophrenia - Preliminary evidence of dissociable transient and sustained deficits. *Schizophrenia Research, 122*(1-3), 104-112. doi: 10.1016/j.schres.2010.03.019

Cerella, J. (1985). Age-related decline in extrafoveal letter perception. *J Gerontol, 40*(6), 727-736.

Chen, Y., Nakayama, K., Levy, D. L., Matthysse, S., & Holzman, P. S. (1999). Psychophysical isolation of a motion-processing deficit in schizophrenics and their relatives and its association with impaired smooth pursuit. *Proc Natl Acad Sci U S A, 96*(8), 4724-4729.

Corbetta, M., Miezin, F. M., Dobmeyer, S., Shulman, G. L., & Petersen, S. E. (1990). Attentional modulation of neural processing of shape, color, and velocity in humans. *Science, 248*(4962), 1556-1559.

Courchesne, E., Townsend, J., Akshoomoff, N. A., Saitoh, O., Yeung-Courchesne, R., Lincoln, A. J., . . . Lau, L. (1994). Impairment in shifting attention in autistic and cerebellar patients. *Behavioral Neuroscience, 108*, 848-865.

De Gelder, B., Vroomen, J., & Van der Heide, L. (1991). Face recognition and lip-reading in autism. *European Journal of Cognitive Psychology, 3*(69-86).

DiLollo, V., Hanson, D., & McIntyre, J. S. (1983). Initiatal stages of visual information processing in dyslexia. *Journal of Experimental Psychology: Human Perception and Performance, 9*, 923-935.

Donohue, S. E., Darling, E. F., & Mitroff, S. R. (2012). Links between multisensory processing and autism. *Exp Brain Res, 222*(4), 377-387. doi: 10.1007/s00221-012-3223-4

Doyle, M. C., & Snowden, R. J. (2001). Identification of visual stimuli is improved by accompanying auditory stimuli: The role of eye movements and sound location. *Perception, 30*(7), 795-810.

Facoetti, A., Paganoni, P., & Lorusso, M. L. (2000). The spatial distribution of visual attention in developmental dyslexia. *Experimental Brain Research, 132*, 531-538.

Farmer, M. E., & Klein, R. M. (1995). The evidence for a temporal processing deficit linked to dyslexia: A Review. *Psychonomic Bulletin & Review, 2*(4), 460-493. doi: 10.3758/bf03210983

Fioravanti, M., Carlone, O., Vitale, B., Cinti, M. E., & Clare, L. (2005). A meta-analysis of cognitive deficits in adults with a diagnosis of schizophrenia. *Neuropsychology Review, 15*(2), 73-95. doi: 10.1007/s11065-005-6254-9

Foucher, J. R., Lacambre, M., Pham, B.-T., Giersch, A., & Elliott, M. A. (2007). Low time resolution in schizophrenia. Lengthened windows of simultaneity for visual, auditory and bimodal stimuli. *Schizophrenia Research, 97*, 118-127.

Frith, U. (1989). *Autism: Explaining the enigma*. Malden, MA: Blackwell Publishing.

Green, M. F., Nuechterlein, K. H., & Breitmeyer, B. (1997). Backward masking performance in unaffected siblings of schizophrenic patients. Evidence for a vulnerability indicator. *Arch Gen Psychiatry, 54*(5), 465-472.

Groth, K. E., & Allen, P. A. (2000). Visual attention and aging. *Front Biosci, 5*, D284-297.

Hairston, W. D., Burdette, J. H., Flowers, D. L., Wood, F. B., & Wallace, M. T. (2005). Altered temporal profile of visual-auditory multisensory interactions in dyslexia. *Experimental Brain Research, 166*(3-4), 474-480. doi: 10.1007/s00221-005-2387-6

Hari, R., & Renvall, H. (2001). Impaired processing of rapid stimulus sequences in dyslexia. *Trends in Cognitive Sciences, 5*(12), 525-532.

Hari, R., Renvall, H., & Tanskanen, T. (2001). Left minineglect in dyslexic adults. *Brain, 124*, 1373-1380.

Harvey, P. D., Keefe, R. S., Moskowitz, J., Putnam, K. M., Mohs, R. C., & Davis, K. L. (1990). Attentional markers of vulnerability to schizophrenia: Performance of medicated and unmedicated patients and normals. *Psychiatry Res, 33*(2), 179-188.

Hillock-Dunn, A., & Wallace, M. T. (2012). Developmental changes in the multisensory temporal binding window persist into adolescence. *Developmental Science, 15*(5), 688-696. doi: 10.1111/j.1467-7687.2012.01171.x

Hugenschmidt, C. E., Mozolic, J. L., & Laurienti, P. J. (2009). Suppression of multisensory integration by modality-specific attention in aging. *Neuroreport, 20*(4), 349-353. doi: 10.1097/WNR.0b013e328323ab07

Jáskowski, P., & Rusiak, P. (2008). Temporal order judgment in dyslexia. *Psychological research, 72*, 65-73.

Kastner, S., & Ungerleider, L. G. (2000). Mechanisms of visual attention in the human cortex. *Annu Rev Neurosci, 23*, 315-341. doi: 10.1146/annurev.neuro.23.1.315

Keetels, M., & Vroomen, J. (2005). The role of spatial disparity and hemifields in audio-visual temporal order judgments. *Experimental Brain Research, 167*, 635-640.

Keetels, M., & Vroomen, J. (2008). Tactile--visual temporal ventriloquism: No effect of spatial disparity. *Percept Psychophys, 70*(5), 765-771.

Keetels, M., & Vroomen, J. (2011). Sound affects the speed of visual processing. *Journal of Experimental Psychology-Human Perception and Performance, 37*(3), 699-708. doi: 10.1037/a0020564

Kwakye, L. D., Foss-Feig, J. H., Cascio, C. J., Stone, W. L., & Wallace, M. T. (2011). Altered auditory and multisensory temporal processing in autism spectrum disorders. *Frontiers in integrative neuroscience, 4*, 129.

Kéri, S., & Janka, Z. (2004). Critical evaluation of cognitive dysfunctions as endophenotypes of schizophrenia. *Acta Psychiatr Scand, 110*(2), 83-91. doi: 10.1111/j.1600-0047.2004.00359.x

Laasonen, M., Service, E., & Virsu, V. (2002). Crossmodal temporal order and processing acuity in developmentally dyslexic young adults. *Brain and Language, 80*(3), 340-354. doi: 10.1006/brln.2001.2593

Lewkowicz, D. J. (1996). Perception of auditory-visual temporal synchrony in human infants. *J Exp Psychol Hum Percept Perform, 22*(5), 1094-1106.

Lickliter, R., & Bahrick, L. E. (2000). The development of infant intersensory perception: Advantages of a comparative convergent-operations approach. *Psychological Bulletin, 126*(2), 260-280. doi: 10.1037//0033-2909.126.2.260

Liddle, E. B., Jackson, G. M., Rorden, C., & Jackson, S. R. (2009). Lateralized temporal order judgement in dyslexia. *Neuropsychologia, 47*(14), 3244-3254. doi: 10.1016/j.neuropsychologia.2009.08.007

Madden, D. J., Whiting, W. L., Cabeza, R., & Huettel, S. A. (2004). Age-related preservation of top-down attentional guidance during visual search. *Psychol Aging, 19*(2), 304-309. doi: 10.1037/0882-7974.19.2.304

Magnée, M. J., Oranje, B., Van Engeland, H., Kahn, R. S., & Kemner, C. (2009). Cross-sensory gating in schizophrenia and autism spectrum disorder: EEG evidence for impaired brain connectivity? *Neuropsychologia, 47*(7), 1728-1732. doi: 10.1016/j.neuropsychologia.2009.02.012

Massaro, D. W. (1984). Children's perception of visual and auditory speech. *Child Dev, 55*(5), 1777-1788.

May, J. G., Williams, M. C., & Dunlap, W. P. (1988). Temporal order judgements in good and poor readers. *Neuropsychologia, 26*(6), 917-924.

McGhie, A., & Chapman, J. (1961). Disorders of attention and perception in early schizophrenia. *The British journal of medical psychology, 34*, 103-116.

Morein-Zamir, S., Soto-Faraco, S., & Kingstone, A. (2003). Auditory capture of vision: Examining temporal ventriloquism. *Brain research. Cognitive brain research, 17*(1), 154-163.

Neuchterlein, K. H., Dawson, M. E., Ventura, J., Miklowitz, D., & Konishi, G. (1991). Information-processing anomalies in the early course of schizophrenia and bipolar disorder. *Schizophrenia Research, 5*(3), 195-196. doi: 10.1016/0920-9964(91)90069-4

Paulus, M. P., & Braff, D. L. (2003). Chaos and schizophrenia: Does the method fit the madness? *Biol Psychiatry, 53*(1), 3-11.

Peled, A., Ritsner, M., Hirschmann, S., Geva, A. B., & Modai, I. (2000). Touch feel illusion in schizophrenic patients. *Biological Psychiatry, 48*(11), 1105-1108. doi: 10.1016/s0006-3223(00)00947-1

Posner, M. I., & Driver, J. (1992). The neurobiology of selective attention. *Curr Opin Neurobiol, 2*(2), 165-169.

Posner, M. I., Early, T. S., Reiman, E., Pardo, P. J., & Dhawan, M. (1988). Asymmetries in hemispheric control of attention in schizophrenia. *Arch Gen Psychiatry, 45*(9), 814-821.

Potkin, S. G., Swanson, J. M., Urbanchek, M., Carreon, D., & Bravo, G. (1989). Lateralized deficits in covert shifts of visual attention in chrnoic and never-medicated schizophrenics compared to normal controls. *Schizophrenia Research, 2*, 95.

Powers, A. R., Hillock, A. R., & Wallace, M. T. (2009). Perceptual training narrows the temporal window of multisensory binding. *J Neurosci, 29*(39), 12265-12274. doi: 10.1523/JNEUROSCI.3501-09.2009

Rhodes, M. G. (2004). Age-related differences in performance on the Wisconsin card sorting test: A meta-analytic review. *Psychol Aging, 19*(3), 482-494. doi: 10.1037/0882-7974.19.3.482

Robertson, I. H., Mattingley, J. B., Rorden, C., & Driver, J. (1998). Phasic alerting of neglect patients overcomes their spatial deficit in visual awareness. *Nature, 395*(6698), 169-172.

Scheier, C. R., Nijhawan, R., & Shimojo, S. (1999). Sounds alters visual temporal resolution. *Investigative Ophthalmology & Visual Science, 40*, 4169.

Spence, C., & Driver, J. (1997). On measuring selective attention to an expected sensory modality. *Percept Psychophys, 59*(3), 389-403.

Spence, C., Nicholls, M. E., & Driver, J. (2001). The cost of expecting events in the wrong sensory modality. *Percept Psychophys, 63*(2), 330-336.

Szelag, E., Kowalska, J., Galkowski, T., & Pöppel, E. (2004). Temporal processing deficits in high-functioning children with autism. *British Journal of Psychology, 95*, 269-282.

Talsma, D., Doty, T. J., & Woldorff, M. G. (2007). Selective attention and audiovisual integration: Is attending to both modalities a prerequisite for early integration? *Cereb Cortex, 17*(3), 679-690. doi: 10.1093/cercor/bhk016

Townsend, J., Adamo, M., & Haist, F. (2006). Changing channels: An fMRI study of aging and cross-modal attention shifts. *Neuroimage, 31*(4), 1682-1692. doi: 10.1016/j.neuroimage.2006.01.045

Uhlhaas, P. J., & Singer, W. (2010). Abnormal neural oscillations and synchrony in schizophrenia. *Nat Rev Neurosci, 11*(2), 100-113. doi: 10.1038/nrn2774

Van der Burg, E., Olivers, C. N. L., Bronkhorst, A. W., & Theeuwes, J. (2008a). Audiovisual events capture attention: Evidence from temporal order judgments. *Journal of Vision, 8*(5), 10.

Van der Burg, E., Olivers, C. N. L., Bronkhorst, A. W., & Theeuwes, J. (2008b). Pip and pop: Nonspatial auditory signals improve spatial visual search. *Journal of Experimental Psychology-Human Perception and Performance, 34*(5), 1053-1065. doi: 10.1037/0096-1523.34.5.1053

Van der Burg, E., Talsma, D., Olivers, C. N. L., Hickey, C., & Theeuwes, J. (2011). Early multisensory interactions affect the competition among multiple visual objects. *Neuroimage, 55*(3), 1208-1218. doi: 10.1016/j.neuroimage.2010.12.068

Verhaeghen, P., & Cerella, J. (2002). Aging, executive control, and attention: A review of meta-analyses. *Neurosci Biobehav Rev, 26*(7), 849-857.

Wainwright-Sharp, J. A., & Bryson, S. E. (1993). Visual orienting deficits in high-functioning people with autism. *Journal of Autism and developmental disorders, 23*, 1-13.

Williams, J. H. G., Massaro, D. W., Peel, N. J., Bosseler, A., & Suddendorf, T. (2004). Visual-auditory integration during speech imitation in autism. *Research in Developmental Disabilities, 25*(6), 559-575. doi: 10.1016/j.ridd.2004.01.008

Nederlandse samenvatting

(Summary in Dutch)

Mensen zijn sociale wezens en communicatie en sociale interactie spelen dan ook een grote rol in ons dagelijks leven. Daarbij gaan we er vanuit dat de mensen met wie we communiceren de wereld om ons heen op ongeveer dezelfde wijze waarnemen als wijzelf. Maar is dat wel zo vanzelfsprekend? Ons dagelijks wereldbeeld wordt voor een belangrijk deel bepaald door de informatie die we via onze zintuigen binnen krijgen. Een spreker hoor en zie je bijvoorbeeld op hetzelfde moment: door zowel je oren als je ogen komt informatie het brein binnen. Deze zintuiglijke (ofwel sensorische) informatie wordt vervolgens door onze hersenen gevormd tot een coherente representatie van de omgeving. Dit proces van het koppelen van een mix van sensorische informatie – ook wel multisensorische integratie (MSI) genoemd – is een continu fenomeen dat onze kijk op het leven vormt en is dan ook van cruciaal belang voor ons dagelijkse, sociale en adaptieve gedrag.

Belang van klinisch onderzoek naar multisensorische informatie-verwerking

Een belangrijke vraag in onderzoek naar multisensorische informatieverwerking is wat er gebeurt als de hersenen de mix aan sensorische informatie niet goed kunnen integreren. Een verstoring van deze integratie kan bijvoorbeeld bijdragen aan tekortkomingen in de communicatie. Vermoed wordt dat dit voorkomt bij stoornissen als autisme en schizofrenie. Mensen met autisme of schizofrenie hebben vaak moeite met sociale situaties, mogelijk omdat zij een afwijkend beeld ervaren van wat de ander zegt en/of bedoelt. Om een beter inzicht te krijgen in het atypische (niet alleen sociaal) gedrag van mensen met klinische of psychiatrische problemen is het belangrijk om onderzoek te verrichten naar onderliggende mechanismen en stoornissen die ten grondslag kunnen liggen aan het afwijkend gedrag. In dit proefschrift is onderzoek gedaan naar de audiovisuele informatieverwerking bij verschillende 'studiegroepen': bij mensen met autisme, schizofrenie en dyslexie en bij ouderen. Meer specifiek hebben we met verschillende gedragsexperimenten onderzocht of geluiden in de vorm van korte kliks of piepjes van invloed zijn op de visuele waarneming bij mensen in de verschillende 'studiegroepen'. Met andere woorden, we bestuderen de inter-zintuiglijke waarneming van visuele en auditieve informatie. Vanuit onderzoek met 'gezonde' mensen weten we bijvoorbeeld dat in bepaalde situaties korte kliks de visuele sensitiviteit van temporele orde kan verscherpen, ofwel ons visuele systeem wordt soms beter dankzij hulp van ons auditieve systeem. Er is echter nog relatief weinig bekend over dit soort effecten bij klinische of psychiatrische populaties. Het doel van dit proefschrift is een beter inzicht te krijgen in de audiovisuele integratie bij de verschillende 'studiegroepen' en dit te relateren aan mogelijk onderliggende gebreken van bijvoorbeeld psychische stoornissen.

Schizofrenie en verminderde temporele sensitiviteit

Schizofrenie is een ernstige en complexe psychiatrische ziekte die onder andere wordt gekenmerkt door wanen, hallucinaties, onsamenhangende spaak en ernstig chaotisch gedrag. De stoornis openbaart zich in de jonge volwassenheid en heeft een chronisch verloop met fluctuerende patronen en cognitieve belemmeringen. Schizofrenie heeft vaak ernstige psychische en sociale gevolgen. Naast genetische en omgevingsfactoren die aan de stoornis ten grondslag liggen, biedt hedendaags onderzoek ook groeiend bewijs dat schizofrenie verband houdt met een fundamentele stoornis in de temporele coördinatie van informatieverwerking in de hersenen. Dit leidt tot het disfunctioneren van perceptuele, cognitieve en motorische processen. Daarnaast heeft onderzoek aangetoond dat mensen met schizofrenie afwijkingen vertonen op zowel neuraal als gedragsniveau in een aantal sensorische modaliteiten. Dit zou kunnen leiden tot verminderde multisensorische informatieverwerking. Het merendeel van onderzoek naar multisensorische informatieverwerking in schizofrenie is gericht op de integratie van audiovisuele spraakinformatie en toont aan dat deze integratie verzwakt is bij mensen met schizofrenie. De resultaten van onderzoek naar meer basale, eenvoudige audiovisuele informatieverwerking (bijvoorbeeld klikjes en lampjes) zijn minder eenduidig, maar sommige onderzoeken suggereren een afwijkende tijdsresolutie bij mensen met schizofrenie.

In ons onderzoek naar de audiovisuele informatieverwerking bij mensen met schizofrenie is met een visuele 'Temporal Order Judgment' (TOJ) taak bekeken of er sprake was van verminderde temporele resolutie of sensitiviteit en of de aanwezigheid van geluid deze sensitiviteit kan verbeteren (**Hoofdstuk 2**). Dit is gedaan door gebruik te maken van het 'temporaal buiksprekereffect', waarbij een temporeel conflict wordt gecreëerd door het presenteren van auditieve en visuele stimuli met een korte temporele a-synchronie. In de visuele TOJ taak die hier is gebruikt, houdt dit in dat een korte klik (bijvoorbeeld 100 ms) te horen is voor een lampje en na een lampje. Het typische gevolg in een temporele buiksprekersituatie is dat het geluid de timing van de visuele boodschap 'vangt'. Het lampje wordt dus waargenomen op (of dichtbij) het tijdstip waarop de klik wordt gehoord, waardoor de visuele sensitiviteit voor temporele orde verbetert. Uit ons onderzoek bleek dat mensen met schizofrenie, vergeleken met een controlegroep, meer moeite hadden met het beoordelen van de temporele volgorde van de visuele stimuli (lampjes). Deze resultaten sluiten grotendeels aan bij eerdere onderzoeken waarin afwijkingen in de tijdperceptie bij mensen met schizofrenie worden gevonden. Ons onderzoek laat echter ook zien dat de presentatie van korte kliks eenzelfde positief effect heeft op de temporele sensitiviteit van mensen met schizofrenie als dat dat bij de controlegroep het geval is. Uit deze resultaten kan worden geconcludeerd dat mensen met schizofrenie, vergeleken met de controlegroep, een verminderde visuele temporele sensitiviteit hebben. Doordat zij evenveel temporeel buiksprekereffect vertonen als de controlegroep, is het aannemelijk dat mensen met schizofrenie geen problemen hebben met de audiovisuele integratie van 'eenvoudige' (lampjes en kliks) informatie.

Autisme Spectrum Stoornissen en (audio)visuele temporele informatieverwerking en aandacht

Autisme Spectrum Stoornissen (ASS) worden gekenmerkt door een achterblijvende ontwikkeling in sociale interactie, communicatie en de aanwezigheid van rigide of stereotype gedragspatronen en interesses. Autisme is de meest ernstige vorm van ASS, waaronder ook mildere vormen vallen zoals het syndroom van Asperger en pervasieve ontwikkelingsstoornissen. Hoewel de precieze oorzaak van ASS nog niet bekend is, lijken genetische en omgevingsfactoren een belangrijke rol te spelen. Naast de hierboven genoemde 'klassieke' kenmerken van ASS, komt er de laatste jaren ook steeds meer empirisch bewijs voor afwijkingen in de unisensorische informatieverwerking die uiteindelijk betrokken kunnen zijn bij multisensorische integratie. Een overgroot deel van onderzoek bij ASS is gericht op de verwerking van sociale, emotionele informatie en biedt een verklaring voor problemen met de integratie van dit soort informatie bij mensen met ASS (wat verband kan houden met de problemen met communicatie). Er is echter weinig aandacht voor de onderliggende mechanismen en voorwaarden waaronder multisensorische informatie wordt geïntegreerd bij mensen met ASS.

In onderzoek naar MSI is de algemene overeenstemming dat temporele synchronie de belangrijkste factor is waaronder MSI kan plaatsvinden. Dat wil zeggen dat integratie van informatie uit verschillende zintuigen alleen zal plaatsvinden als deze verschillende informatie ongeveer tegelijkertijd aankomt in de hersenen. Zo niet, dan wordt het als aparte gebeurtenissen waargenomen. Temporele informatieverwerking is dus een belangrijke factor, maar hierover is tot nu toe weinig bekend bij mensen met ASS. Eerdere onderzoeken bieden voornamelijk bewijs dat er mogelijk afwijkingen zijn in de perceptie van temporele audiovisuele informatieverwerking. Onderzoek naar de verwerking van meer eenvoudige audiovisuele informatie is beperkter en minder consistent in de bevindingen.

In **Hoofdstukken 3** en **4** is onderzoek gedaan naar de temporele verwerking van eenvoudige, audiovisuele informatie bij adolescenten met ASS. Allereerst kregen de adolescenten met ASS een audiovisuele TOJ taak aangeboden, waarin zij van verschillende soorten stimuli moesten aangeven of het geluid ten opzichte van de video te vroeg of te laat kwam (**Hoofdstuk 3**). Deze aangeboden stimuli varieerden in complexiteit (een beeld van een gezicht dat /bi/ uitspreekt, een handklap en een klik/lamp). Hiermee konden we onderzoeken of de adolescenten met ASS meer algemene of specifieke moeite zouden hebben met audiovisuele temporele informatieverwerking. Hoewel onze verwachting was dat de adolescenten vooral moeite zouden hebben met het beoordelen van de temporele order van de audiovisuele spraak (/bi/) vanwege de complexiteit en sociale karakter van de stimulus, bleek dit niet het geval. De resultaten lieten zien dat de adolescenten met ASS met alle drie de audiovisuele stimuli meer moeite hadden om de temporele volgorde hiervan te bepalen, vergeleken met een controlegroep. Dit suggereert dat adolescenten met ASS een algemeen probleem hebben met audiovisuele temporele verwerking. Deze bevinding wordt kracht bijgezet door de resultaten van **Hoofdstuk 4**, waarin met een visuele TOJ taak duidelijk werd, dat adolescenten met ASS een verminderde sensitiviteit hebben voor visuele temporele orde vergeleken met een controlegroep. Deze laatste bevinding zou echter (deels) veroorzaakt kunnen worden door eerder gerapporteerde bevindingen dat mensen met ASS problemen hebben met visuele aandacht, met name het losmaken en verplaatsen van deze aandacht. Deze aandachtproblemen zouden gerelateerd kunnen worden aan slechte beoordelingen van visuele temporele orde. Om dit nader te onderzoeken hebben we de adolescenten met ASS een tweetal aandachtstaken voorgelegd, te weten de visuele zoektaak 'pip-en-pop' en een digitale klokleestaak. Met deze taken werd onderzocht of de adolescenten met ASS moeite hadden met het losmaken en/of verplaatsen van de visuele aandacht. Daarnaast werd bestudeerd of het aanbieden van korte kliks de prestaties ten goede kwam. Resultaten wezen uit dat de adolescenten met ASS hetzelfde presteerden op de aandachtstaken als de controlegroep en suggereren dus geen problemen met het losmaken en/of verplaatsen van aandacht bij adolescenten met ASS. Een andere belangrijke bevinding was dat de prestaties van adolescenten met ASS verbeterden door de aanwezigheid van geluid (korte kliks) in alle taken, net zoals de controlegroep. Kortom, ons onderzoek wijst uit dat adolescenten met ASS specifieke problemen hebben met (audio)visuele temporele sensitiviteit voor synchronie of orde, zonder moeite te hebben met visueel zoeken of oriënteren. Daarnaast hebben adolescenten profijt van de aanwezigheid van korte kliks – hun visuele prestaties verbeterden – zoals dat bij de controlegroep het geval is. Dit toont duidelijk aan dat adolescenten met ASS geen algemene stoornis vertonen in de multisensorische integratie van eenvoudige audiovisuele informatie.

De invloed van geluid op visueel zoekgedrag bij mensen met dyslexie

Dyslexie is een neurobiologische stoornis die gekenmerkt wordt door problemen met lezen en spelling, ondanks voldoende intelligentie, scholing en motivatie. Naast hun fonologische problemen ervaren mensen met dyslexie ook vaak een variëteit aan subtiele sensorische of motorische gebreken, maar het is nog onbekend of deze problematiek gerelateerd is aan de leesstoornis of op zichzelf staan. Er bestaan diverse hypotheses omtrent de oorzaak van dyslexie, zoals problemen met auditieve of temporele informatieverwerking of de 'Sluggish Attentional Shifting' (SAS) hypothese. In deze laatste hypothese wordt er vanuit gegaan dat mensen met dyslexie moeite hebben om hun aandacht los te maken van waar deze op is gericht. Diverse studies waarin de visuele aandacht van mensen met dyslexie onderzocht is, bevestigen deze visuele aandachts-problematiek, hetgeen zich uit in bijvoorbeeld lange zoektijden. In ons onderzoek (**Hoofdstuk 5**) zijn wij verder ingegaan op de mogelijke visuele aandachtsproblemen bij mensen met dyslexie en hebben wij tevens de hypothese getoetst of de aanwezigheid van geluid de visuele prestatie van mensen met dyslexie kan verbeteren. Deelnemers aan dit onderzoek kregen de visuele zoektaak 'pip-en-pop' aangeboden. In deze taak wordt mensen gevraagd om *een horizontaal of verticaal* ('target') lijntje te zoeken tussen meerdere diagonale lijntjes ('setgrootte' 24 of 48). Tijdens dit experiment knipperden een aantal lijntjes van kleur (van groen naar rood en vice versa). Ook het target veranderde van kleur. Dit was echter op dat moment de enige kleurverandering. In de helft van de gevallen werd de kleurverandering van het target begeleid door een simpel klik-geluid. Eerder onderzoek met deze taak heeft aangetoond dat het zoeken naar het target een moeilijke taak is en dat de zoektijd oploopt naarmate het aantal diagonale lijntjes in de omgeving toeneemt (de setgrootte). In de gevallen dat het klik-geluid gelijk viel met de kleurverandering van het target, werd deze veel sneller gevonden, onafhankelijk van het aantal omringende lijntjes. Dit effect wordt het 'pip-en-pop' effect genoemd; het lijkt of het klik-geluidje (in Engels de 'pip') je de indruk geeft dat het target eruit springt, ofwel de 'pop-out'. De resultaten van ons onderzoek laten een aantal interessante zaken zien. (1) De zoektijd van het target in de gevallen zonder geluid is bij mensen met dyslexie veel langer dan die van 'normale' lezers, (2) vergeleken met 'normale' lezers wordt de zoektijd in de geluidafwezige gevallen bij mensen met dyslexie langer als de setgrootte van de lijntjes vergroot, en (3) de zoektijd van mensen met dyslexie verbetert ingrijpend door de aanwezigheid van het klik-geluid, zelfs tot hetzelfde niveau als dat van de controlegroep. Daarmee tonen we met ons onderzoek aan dat mensen met dyslexie afwijkend visuele zoekgedrag vertonen, wat gezien kan worden als bewijs dat zij moeite hebben met het verplaatsen of losmaken van de visuele aandacht. Opmerkelijk genoeg kunnen deze problemen overwonnen worden door de aanwezigheid van een klik-geluid.

Multisensorische informatieverwerking bij ouderen

Behalve dat er als gevolg van neurobiologische of psychiatrische stoornissen problemen met MSI kunnen optreden, is het interessant te onderzoeken of MSI ook onderhevig is aan het verouderingsproces van de mens. Diverse ontwikkelingsstudies hebben bewijs gevonden dat het ouder worden met aanzienlijke veranderingen in de multisensorische temporele informatieverwerking gepaard gaat. Als we ouder worden, vinden er niet alleen grote veranderingen plaats in het zintuiglijke systeem (bijvoorbeeld moeite met lezen, verminderd gehoor) en cognitieve systeem (bijvoorbeeld geheugen, concentratie), maar ook in het verouderende brein (bijvoorbeeld veranderingen in het neurostransmitter systeem). Hoewel de algemene consensus is dat er sprake is van verslechtering van de sensorische processen bij ouderen, is er volop debat over de vraag of MSI intact is of aangetast is bij ouderen. In ons onderzoek zijn we op deze vraag ingegaan en hebben we vijf leeftijdsgroepen (20-ers tot en met 60-jarigen) onderzocht op hun sensitiviteit van visuele, auditieve en audiovisuele temporele orde (**Hoofdstuk 6**) door middel van een visuele, auditieve en audiovisuele TOJ taak. De resultaten van ons onderzoek brengen drie belangrijke punten aan het licht. Allereerst heeft ouder worden een nadelig effect op de sensitiviteit voor auditieve, visuele en audiovisuele temporele orde. Dit wordt merkbaar rond de leeftijd van 50 jaar. Daarnaast is MSI niet verminderd bij ouderen, maar kan het juist als compenserend mechanisme werken om de nadelige effecten van leeftijd te verminderen (de verminderde sensitiviteit voor visuele temporele orde verbetert immers met de aanwezigheid van klik-geluidjes). Tot slot vonden we dat sensitiviteit voor audiovisuele temporele orde niet correleert met MSI, hetgeen suggereert dat goed geconserveerde oordelen over crossmodale temporele orde niet noodzakelijk is om MSI te laten plaatsvinden

Conclusie

Het overkoepelende doel van dit proefschrift was een bijdrage te leveren aan de kennis op het gebied van audiovisuele integratie van eenvoudige informatie bij mensen met ASS, schizofrenie en dyslexie en bij ouderen. Samenvattend zijn de drie belangrijkste bevindingen van de verschillende onderzoeken die in deze thesis beschreven worden (1) de visuele, temporele informatieverwerking is verminderd bij mensen met ASS, schizofrenie en dyslexie en ouderen, (2) dit visuele informatieverwerkingsprobleem kan gecompenseerd worden door geluid, aangezien klik-geluidjes een bevorderlijke, 'rehabiliterende' werking hebben op de visuele informatieverwerking van alle onderzochte studiegroepen en (3) gezien deze verbeteringen van visuele temporele informatieverwerking door de aanwezigheid van geluid, kan verondersteld worden dat de integratie van eenvoudige, audiovisuele informatie bij mensen met ASS, schizofrenie en dyslexie en ouderen intact is.

Dankwoord

(Acknowledgments)

Dankwoord (Acknowledgments)

Dit proefschrift is het resultaat van vijf boeiende, leerzame, soms frustrerende, maar vooral uitdagende en gezellige jaren. Tijdens deze bijzondere periode heb ik met veel mensen kennisgemaakt en samengewerkt. Mensen die ieder op eigen, vaak inspirerende, wijze een bijdrage hebben geleverd aan dit proefschrift. Graag wil ik dit dankwoord aan hen richten.

Mijn grootste dank gaat uit naar alle mensen die deel hebben willen nemen aan de verschillende onderzoeken. Dankjewel voor jullie inzet en enthousiasme! Ik hecht erg veel waarde aan jullie (soms ontroerende) eerlijkheid, openheid en positiviteit die tijdens de informele gesprekken tussen het testen door naar voren kwamen.

Jean, zonder jou was deze thesis nooit door mij geschreven. Dankzij alle ruimte en vrijheid die je me hebt gegeven, maar met altijd een kritische blik (en een 'tikkeltje' ongeduld) op de achtergrond, gaf je mij het vertrouwen om van ons mooie project een succes te maken. Dankjewel! Ik heb respect voor je snelle manier van denken en schakelen en je enorme kennis en expertise.

Miriam, dankjewel dat je altijd voor me klaar stond voor hulp en praktische inzichten. Door jouw doelgerichte vragen en opmerkingen bracht je mijn soms afgeleide blik weer terug naar de kern. Maar vooral ook veel dank voor het geklets en gelach.

Graag wil de leden van mijn promotiecommissie bedanken. Prof. dr. C. Kemner, prof. dr. M.M. Sitskoorn en dr. D. Talsma, hartelijk dank voor de tijd en moeite die jullie in de warme zomerperiode hebben besteed aan het lezen van mijn proefschrift.

Co-auteurs Jan Pieter Maes, Arthur van Gool en Mart Eussen, heel erg bedankt voor jullie inzet, kritische en opbouwende commentaren, hulp bij diagnostische en patiënt-gerelateerde vraagstukken en altijd positieve houding.

Sandra Kint, Ad van der Sijde, Tjaddie van der Hoek, Janny Mulder, Joram van Immerzeel, Petra Kolvenbach en sociotherapeuten van De Steiger – Yulius, enorm bedankt voor al jullie tijd en moeite bij het benaderen, informeren en inplannen van de jongeren en voor jullie warme gastvrijheid.

Prof. dr. Kees Brunia, heel erg bedankt voor alle hulp en de samenwerking bij het Parkinson onderzoek.

Jeroen, jouw humor maakt altijd alles weer goed. Ruud en Lisanne, dankjewel voor alle gezelligheid. Alle andere collega's, bedankt voor de gezellige tijd.

Mijn 'roomies'; Martijn, partner-in-crime, ik ben je tot op mijn laatste dag blijven missen. Carlijn, dagelijkse, hilarische, ontroerende, ons-tot-in-de-nacht-wakker-houdende en frustrerende zaken, we hebben het allemaal besproken. Ikram, de tijd op een kamer was kort, maar warm en gezellig. Marlies, lang geleden, maar met veel goede herinneringen.

Karin, dankjewel voor de mooie lay-out van dit proefschrift en voor al het werk dat je me uit handen hebt genomen.

Lieve paranimfen Simone en Marjolein, wat een fijn en geruststellend gevoel dat jullie 'achter' mij staan 1 november. Simone, ik word blij van jouw opgewektheid en het enthousiasme waarmee je onderzoek verricht. Wat was het fijn dat je zoveel jaren op donderdag op onze kamer zat. Dankjewel voor de warme vriendschap die we hebben opgebouwd. Lieve Lein, al 20 jaar vriendinnen, wat een voorrecht. Onze mooie levens en gezinnen lopen zo parallel aan elkaar en we hebben vaak aan een blik genoeg. Dankjewel dat ik altijd bij je terecht kan.

Allerliefste papa en mama, dankjewel voor de gezellige en warme thuishaven, liefde en steun door alle jaren heen en jullie onuitputtelijke oppasenergie!

Allerliefste Morten, Tiemen en Josefiene, jullie zijn mijn heerlijke schatten en maken mij iedere dag weer (gek ☺ en) gelukkig. Wees trots op wie je bent en durf je dromen te leven.

Allerliefste Peter, dankjewel voor je verbluffende relativeringsvermogen, onverwoestbare relaxedheid en grenzeloze geduld! TA